Synthetic Strategies to Access Biologically Important Fluorinated Motifs:

Fluoroalkenes and Difluoroketones

By

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Abstract

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

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

α,α-difluoroketones represent a privileged substructure in medicinal chemistry, and serves as inhibitors to many hydrolytic enzymes, such as serine and aspartyl proteases. From chapters 3 to 5, palladium-catalyzed decarboxylative methods are developed for accessing α-alkyl- and α-aryl-α,α-difluoroketones. This decarboxylative strategy overcomes two major challenges associated with alkylation reactions of α,α-difluoroketone enolates. Chapter 3 demonstrates that decarboxylation regioselectively generates α,α-difluoroketone enolates, which are difficult to access by base

deprotonation. Moreover, palladium catalysis enables the coupling of the α,α-difluoroketone enolate with benzylic electrophiles to form a key C(α)–C(sp^3) bond. In chapter 4, an orthogonal catalytic system is developed for accessing linear and branched α-allyl-α,α-difluoroketones. Two distinct mechanisms are involved in the formation of the regioisomers. Chapter 5 describes a base-mediated selective *para*-C–H difluoroalkylation of arenes, which represents a different strategy for *para*-C–H functionalization of arenes compared to the known methods. These decarboxylative coupling reactions provide structurally diverse α,α-difluoroketone derivatives, and should be useful for accessing potential biological probes and therapeutics.

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Abbreviations

Ac	acetyl
Acac	acetylacetone
aq	aqueous
Ar	aryl (substituted aromatic ring)
Asp	aspartic acid
BBN	9-borabicyclo[3.3.1]nonane
BEt_3	triethylborane
BINAP	2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
BSA	*N*,*O*-*bis*(trimethylsilyl)acetamide
Bu	butyl
Bu_3Sn	tributyltin
Bz	benzoyl
ca	circa (approximately)
calcd	calculated
cat.	catalytic
CF_3	trifluoromethyl
CO_2	carbon dioxide
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine

DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-*bis*(diphenylphosphino)ethane
dppf	1,1′-*bis*(diphenylphosphino)ferrocene
dppp	1,3-*bis*(diphenylphosphino)propane
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Et	ethyl
EWG	electron-withdrawing group
GABA	gamma-aminobutyric acid
Het	heteroaromatic
His	histidine
HMPA	hexamethylphosphoric acid triamide
i	iso
IBX	*o*-iodoxybenzoic acid
KHMDS	potassium *bis*(trimethylsilyl)amide
L_n	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
lit.	literature value (abbreviation used with period)
MAD	methyl aluminum *bis*(2,6-di-*t*-butyl-4-methylphenoxide)
Me	methyl
MeOH	methanol
Mes	mesityl
2-Me-THF	2-methyltetrahydrofuran
mp	melting point
NaH	sodium hydride
NaHMDS	sodium *bis*(trimethylsilyl)amide
n	normal (e.g. unbranched alkyl chain)
NBS	*N*-bromosuccinimide

n-BuLi	*n*-butyllithium
Nu	nucleophile
OMe	methoxy
Pd	palladium
Ph	phenyl
phen	9,10-phenanthroline
PPh_3	triphenylphosphine
Pr	propyl
rac	racemic
rt	room temperature
sec	secondary
Ser	serine
S_N2	bimolecular nucleophilic substitution
S_N1	unimolecular nucleophilic substitution
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tc	thiophene-2-carboxylate
TEA	triethylamine
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Th	2-thienyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	*p*-tolyl
Trisyl	2,4,6-triisopropylbenzenesulfonyl
Ts	*p*-toluenesulfony

Chapter 1. Importance and Application of Fluorine in Drug Design

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

Fluorine plays an important role in the campaign of drug discovery, because of some unique features imparted by fluorine. For example, the use of fluorine and fluorinated groups as isosteres in drug design,[5] (i.e., F vs H, CF_3 vs *i*-Bu, and CF_2Me vs OMe), can modulate molecular properties, including the lipophilicity and conformations, and improve metabolic stability. Moreover, the incorporation of fluorine into small molecule drugs modifies ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, in which it is possible to convert a bad drug candidate to a potential therapeutic. Because of these potential applications of fluorine on drug design, the following sections elaborate the influence of fluorine substitution on physicochemical properties, molecular conformations, metabolic stability, binding affinity, and potency of therapeutic agents.

1.1 The Effect of F on Physicochemical Properties

Fluorine is the most electronegative element (χ = 4.0), and its incorporation into molecules strongly affects the acidity or basicity of the neighboring groups, thus lowering pK_a values (Table 1.1).[5,6]

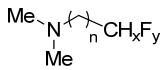
Table 1.1. The Effect of Fluorine Substitution on pK_a of Acids, Alcohols, Phenols, Anilines, and Amines

acid	pK_a	alcohol	pK_a	phenol	pK_a	aniline	pK_a	amine	pK_a
CF_3CO_2H	0.5	$(CF_3)_3COH$	5.4	C_6F_5OH	5.5	$C_6F_5NH_2$	–0.36	$CF_3CH_2NH_2$	5.7
CHF_2CO_2H	1.3	$(CF_3)_2CHOH$	9.3	C_6H_5OH	10.0	$C_6H_5NH_2$	4.6	$CHF_2CH_2NH_2$	7.3
CH_2FCO_2H	2.6	CF_3CH_2OH	12.4					$CH_2FCH_2NH_2$	9.0
CH_3CO_2H	4.8	CH_3CH_2OH	15.9					$CH_3CH_2NH_2$	10.7

The σ-inductive effect of fluorine atoms decreases the basicity of the amine group. For acyclic amines, the extent of pK_a change depends on the distance of fluorine to the amine group, and the number of fluorine atoms.[7] For example, in the case of alkyl amines, the pK_a is lowered by 1.7 for β-F, and by 0.3 for δ-F, thus demonstrating the impact of the fluorinated position on the pK_a shift (Table 1.2A). Moreover, the trifluoroethyl amine has an attenuated pK_a of 5.7 due to the additive effect of three F atoms compared to the monofluoroethyl amine with a pK_a of 9.0 (Table 1.2B). However, the influence of fluorine on basicity of cyclic amines also requires the consideration of conformational factors (axial F vs. equatorial F) in addition to the calculation of distances of fluorine to amine functionality (Table 1.2C).[7] For example, in the case of 3-fluoropiperidine, an equatorial F substituent causes a pK_a shift of 2.3 ($\Delta pK_a = -2.3$), while an axial F substituent only reduces pK_a of 1.4 ($\Delta pK_a = -1.4$). This pK_a difference between these two conformations of 3-fluoropiperidine derives from a preferential conformation of the protonated base, in which the dipole of the $H–N^+$ bond presents antiparallel to the dipole of the C–F bond. This conformational alignment stabilizes protonated 3-fluoropiperidine, thus causing a higher pK_a value and smaller ΔpK_a. Similarly, fluorine on an axial or equatorial position of 4-fluoropiperidine also causes different pK_a change with ΔpK_a of –1.7 for an axial F atom and ΔpK_a of –0.9 for an equatorial F atom. Moreover, for aromatic amines, pK_a alteration by fluorine depends on the position of fluorine atoms and the degree of fluorination (Table 1.2D). Generally, fluorine on an *ortho*-position causes a larger impact on pK_a than a *meta*-F atom does (pK_a of **1** < pK_a of **2**; pK_a of **3** < pK_a of **4**), and highly fluorinated amines have lower pK_a than mono- or difluorinated counterparts (pK_a of **1** > pK_a of **3**; pK_a of **2** > pK_a of **4**).

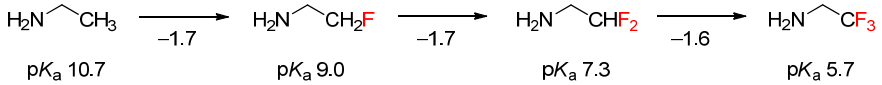
Table 1.2. Fluorination Affects Basicity of Amines

A) The Influence of F on pK_a by the Distance of F to Amine Functionality

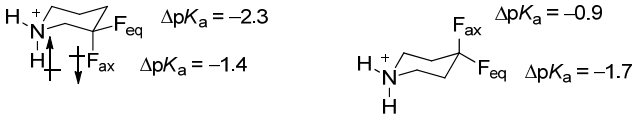


n	F position	ΔpK_a
1	β-F	–1.7
2	γ-F	–0.7
3	δ-F	–0.3
4	ε-F	–0.1

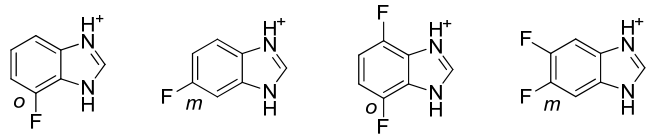
B) The Influence of F on pK_a by Fluorination



C) The Influence of F on pK_a of Cyclic Amines by Conformational Effect

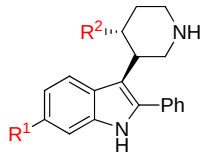


D) *ortho*-Fluorine Affected pK_a More Than *meta*-Fluorine



The perturbation of pK_a alters pharmacokinetic properties of drug candidates. For example, alkyl amines, anilines and *N*-containing heterocycles are common structural components in bioactive molecules or drug candidates. However, excessive number of basic amine groups in the amine-containing therapeutics cause low oral bioavailability, which decreases the potency and limits their development as potential drugs. To modulate these properties, the introduction of fluorine in *N*-bearing molecules decreases the basicity of the amine groups by the inductive effect and improves the bioavailability,[7] as exemplified in the case of 3-piperidinylindole antipsychotics (Table 1.3).[6a,8] These fluorinated analogues express much better bioavailability than the non-fluorinated counterpart. Thus, fluorine substitution can be utilized in tuning the basicity of amine-type molecules in drug design to achieve the expected physicochemical properties and distribution.[6a,8]

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

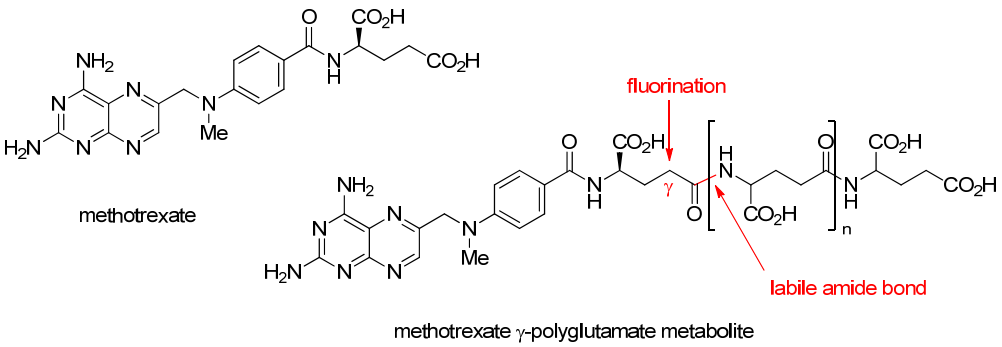


R^1, R^2	5-HT_{2A} (nM)	pK_a	F (%)
H, H	0.99	10.4	poor
H, F	0.43	8.5	18
F, F	0.06	-	80

On the other hand, fluorine substitution increases the acidity of carboxylic acids and phenol derivatives, and changes physicochemical features that can also bring beneficial applications to drug design. For example, methotrexate is used to treat rheumatoid arthritis and cancer, but it possesses high toxicity associated with the formation of poly-γ-glutamate metabolites. Fluorination of the γ-glutamate moiety of methotrexate increases the acidity of γ-carboxyl group and causes labile amide linkages, which disfavor the accumulation of poly-γ-glutamate metabolites inside the cells, and significantly reduce the toxicity (Figure 1.1A).[9a] Another example is the utilization of 2,6-difluorophenol as a lipophilic isostere of a carboxylic acid. The inductive effect of two fluorine atoms remarkably reduces pK_a of 2,6-difluorophenol to 7.1 from pK_a of 9.8 of phenol, and causes its ionization to form phenoxides at pH = 8.5, where a carboxylic acid also exists as the ionized form (Figure 1.1B).[9b] Thus, 2,6-difluorophenols can efficiently mimic a carboxylic acid functionality, and this idea has been applied in designing inhibitors of GABA aminotransferases.

Figure 1.1. Effect of Fluorination on Physicochemical Properties and Applications on Drug Design

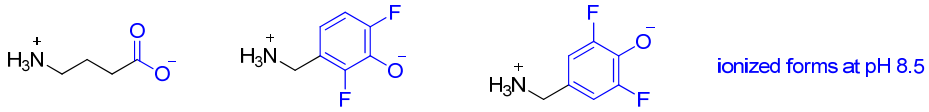
A) Fluorination Disfavors Polyglutamylation and Decreases Toxicity



methotrexate

methotrexate γ-polyglutamate metabolite

B) Fluorinated Phenol Mimics a Carboxylic Acid



GABA

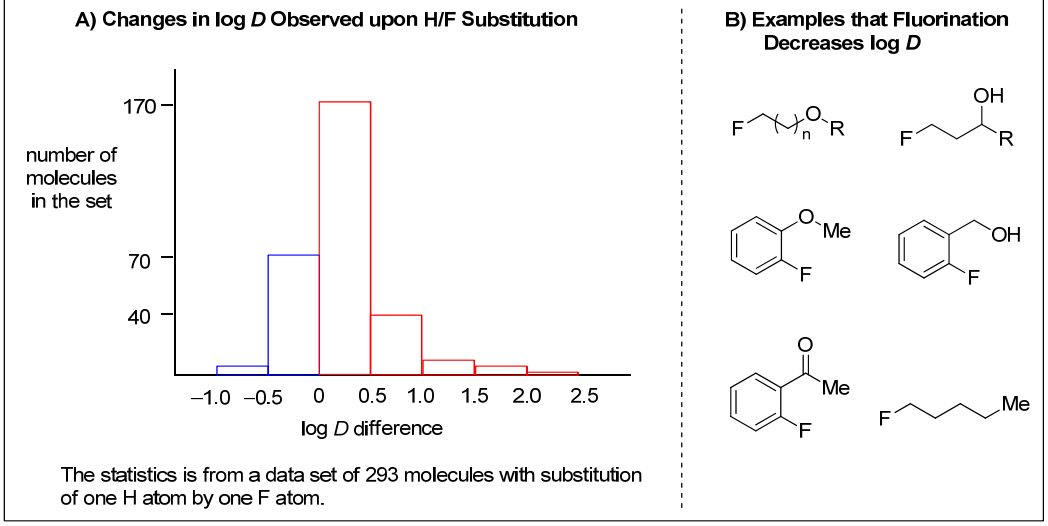
2,6-difluorophenols

1.2 The Effect of F on Lipophilicity

Lipophilicity is an important parameter in evaluating drug-like molecules.[10] This property affects the absorption of orally administrated drugs into the intestinal system, protein-ligand non-specific binding interactions, and the solubility. High lipophilicity increases oral absorption of drugs and lipophilic binding interactions, but excessive lipophilicity can also cause poor solubility and undesired side effects. Thus, moderate lipophilicity is required for ideal drugs. Fluorine substitution can modulate molecular lipophilicity, as shown in Figure 1.2.[11a] Generally, the incorporation of fluorine into the molecules increases the lipophilicity (positive log *D* difference in Figure 1.2A). Herein, log *D* means the logarithmic coefficient of the distribution of a charge-bearing molecule between water and octanol at a specific pH. Increased lipophilicity usually occurs in molecules bearing fluorine adjacent to a π system, such as aryl or vinyl fluorides.[11a,b] In these molecules bearing C(sp^2)–F bonds, good overlap of lone pair orbitals of fluorine with π^* orbital of the C=C bond depolarizes the C–F bond and decreases molecular polarity.[11a,b] However, in some cases, fluorine substitution actually decreases the lipophilicity (negative log *D* difference in Figure 1.2A). Specifically, the presence of fluorine close to an oxygen atom polarizes the

adjacent oxygen atom and enhances the solvation of the molecule in water, thus leading to a decrease of the lipophilicity (Figure 1.2B).[11a,b] Moreover, the strong electron-withdrawing effect of fluorine atoms polarizes C–F bonds of saturated fluoroalkanes, which decreases lipophilicity compared to their non-fluorinated counterparts.[11b,c]

Figure 1.2. Fluorine Substitution Modifies Molecular Lipophilicity



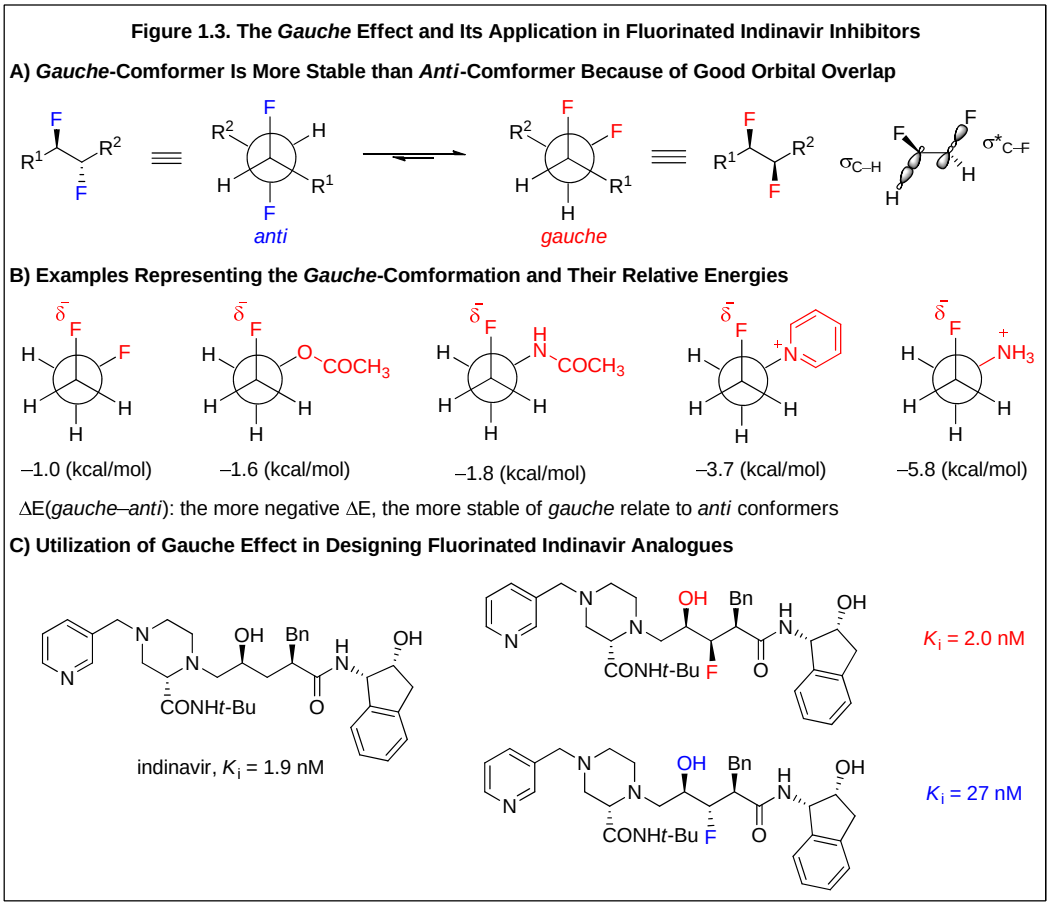
1.3 The Effect of F on Molecular Conformations

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

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

been applied in designing fluorinated analogues of HIV-1 protease inhibitor indinavir with comparable inhibitory activity (Figure 1.3C).[13]

Figure 1.3. The *Gauche* Effect and Its Application in Fluorinated Indinavir Inhibitors

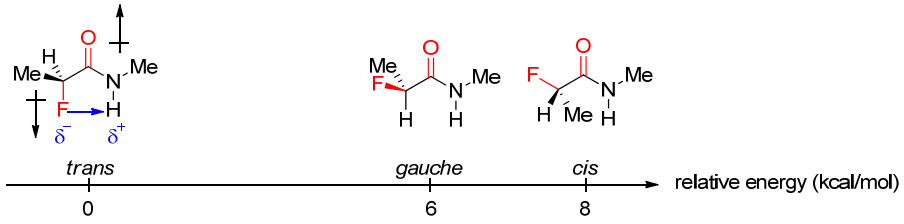


However, the *gauche* arrangement is not always the preferential conformation for some fluorinated molecules. For example, *N*-β-fluoroethylamides (F–C–C–NHC=O) prefer the gauche conformation,[14a,b] while α-fluoroamides (F–C–C=O–NH) prefer to exist in the *trans* conformation.[14a,c] In these cases, the *trans* conformer is more stable than the *gauche* conformer by 6 kcal/mol, due to the synergistic dipole-dipole interaction between the C–F and C=O bonds, and the electrostatic interaction between electronegative F atom and electropositive H atom of the amide bond (Figure 1.4A).[14a,c] Such a conformational perturbation due to fluorine substitution near an amide has been applied to probe the bioactive conformation of an amide ligand bound to the target protein. As in the case of fluorinated ligands for the calcitonin gene-related peptide receptor(CGRP), the two regioisomers, both of which bear a fluorine atom adjacent to the amide bond, represent distinct CGRP binding affinity (Figure 1.4B).[15] The

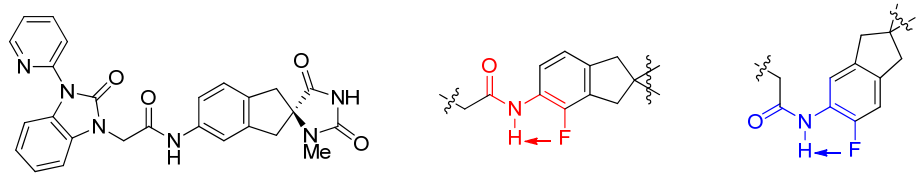
extended structure expresses lower K_i (red color in Figure 1.4B), and it is the bioactive conformation that the ligand adapts when binding to the CGRP receptor. The conformational information in protein-ligand binding modes enables development of more potent CGRP inhibitors.

Figure 1.4. Fluorine Substitution Impacts Molecular Conformation and the Potency

A) Calculated Related Rotational Energy of Conformers of *N*-Methyl-2-fluoropropionamide



B) Fluorine Substitution to Probe Bioactive Conformation of the Ligand Bound to CGRP

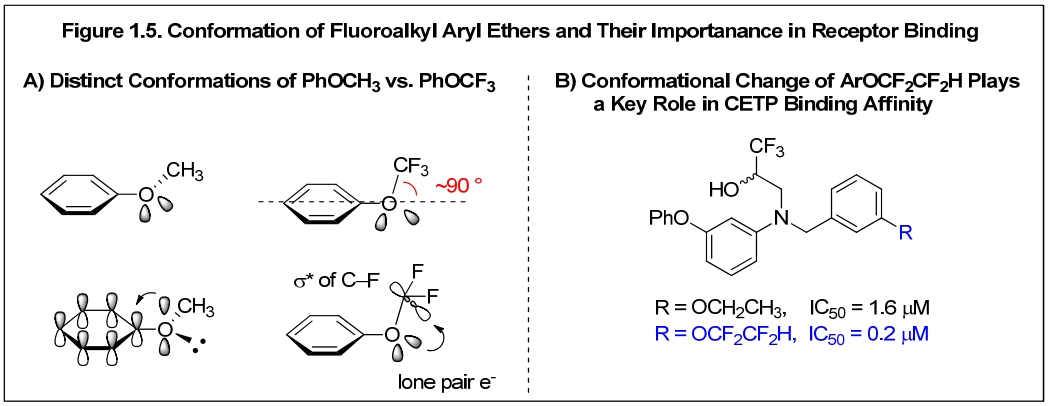


CGRP K_i = 20 nM | CGRP K_i = 55 nM | CGRP K_i = 720 nM

Moreover, the introduction of trifluoromethyl or difluoromethene groups on a heteroatom also changes molecular structures. For example, the three-dimensional structures of fluorinated alkyl aryl ethers (Ar-OCF_3 or Ar-OCF_2H) are different from their non-fluorinated counterparts (Ar-OCH_3). Specifically, anisole ($PhOCH_3$) adapts a planar conformation, in which the methoxy group is coplanar with the phenyl ring (left, Figure 1.5A).[16 a] The planar conformation comes from the resonance stabilization of lone pair electrons of the oxygen atom into the phenyl ring. In contrast, the trifluoroanisole counterpart ($PhOCF_3$) adapts a non-planar conformation, in which the trifluoromethoxy group is orthogonal to the plane of the phenyl ring (right, Figure 1.5A).[16b–d] This conformational change is attributed to the decreased resonance stabilization of oxygen lone pair electrons into the phenyl ring as a result of the hyperconjugation between lone-pair orbitals of the O atom and low-lying σ^* orbitals of C–F bonds and the inductive effect of the CF_3 group. The same conformational alteration due to fluorination also occurs in difluoroanisoles ($PhOCF_2H$), but they represent more flexible conformational exchange between the coplanar and perpendicular structures.[16d,e] Such a conformational modification of fluoroalkyl

aryl ethers plays an important role in protein-ligand binding interactions, and has been exploited in drug design. As in the case of developing potent inhibitors of the cholesteryl ester transfer protein (CETP) to reduce the incidence of coronary heart disease, the tetrafluoroethyl substituted analog reveals an 8-fold increase in the CETP inhibitory activity compared to ethyl substituted counterparts (Figure 1.5B).[17]

Figure 1.5. Conformation of Fluoroalkyl Aryl Ethers and Their Importanance in Receptor Binding



1.4 The Effect of F on Metabolic or in vivo Stability

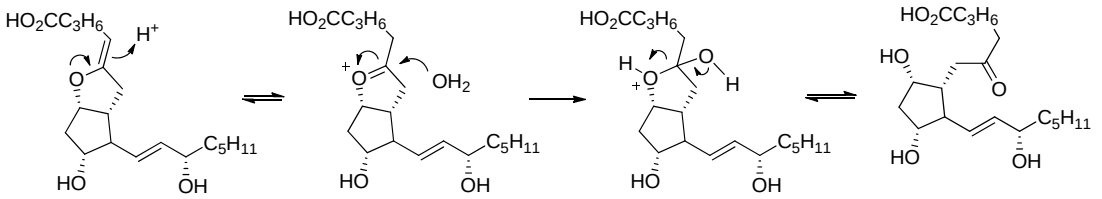
The metabolic or *in vivo* stability, expressed as the half-life, is a key factor in determining a successful drug molecule. An ideal and safe drug should possess a moderate half-life that enables it to reach the action site, maintain efficient drug concentration for a desired period of time, and be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

An example demonstrating the impact of fluorination on chemical stability of potential therapeutics involves prostacyclins. Prostacyclin inhibits platelet aggregation, but has limited clinical application due to the *in vivo* degradation. The chemical instability derives from the presence of the enol ether functionality in the molecule, which undergoes hydrolysis to form inactive metabolites under neutral or acidic conditions (Figure 1.6A),[19a] thus revealing a $t_{1/2}$ = 10 mins at pH = 7.4. However, fluorine introduction on the position adjacent to the enol ether destabilizes the cationic intermediate formed during

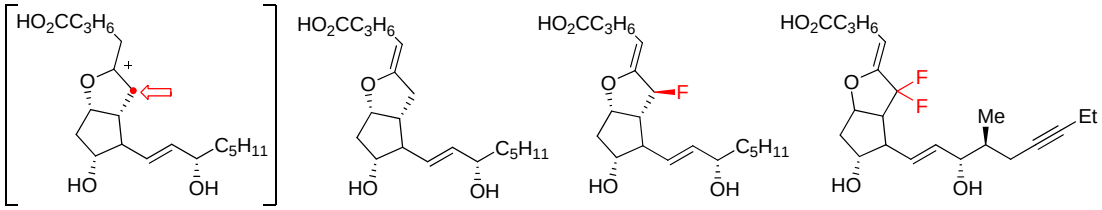
hydrolysis, and enhances chemical stability *in vivo*, as represented $t_{1/2}$ > 1 month at pH = 7.4 for monofluorinated analog[19b] and $t_{1/2}$ = 90 days at pH = 7.4 for difluorinated analog (Figure 1.6B).[19c]

Figure 1.6. Fluorine Substitution Stabilizes Prostacyclins against Acidic Degradation

A) Acidic Hydrolysis of Prostacyclin *in vivo*



B) Fluorine Substitution Enhances the Stability of Prostacyclins against Acidic Hydrolysis



Fluorine substitution disfavors formation of unstable cation during hydrolysis, thus extending $t_{1/2}$

$t_{1/2}$ = 10 mins

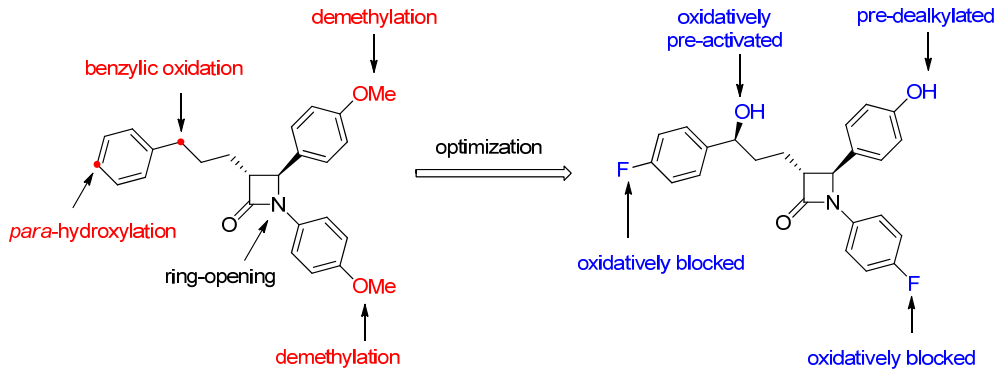
$t_{1/2}$ > 1 month

$t_{1/2}$ = 90 days

$t_{1/2}$ means chemical half-life at pH = 7.4

The improved efficacy as a result of fluorine substitution to block metabolic pathways is exemplified in the development of Ezetimibe as a cholesterol-lowering agent (Figure 1.7).[20] Initially, the lead underwent extensive CYP450-catalyzed metabolism, including benzylic oxidation, *para*-hydroxylation of the aromatic ring, dealkylation of two OMe groups, and ring-opening of the cyclic lactam to produce many metabolites. Thus, high doses were required to maintain sustained *in vivo* action (left in Figure 1.7, shown in red color). SAR studies found that some of the metabolites are more potent than the parent drug (oxidative activation), while some of them are not (oxidative deactivation). The redesign of the drug aims on installing beneficial groups that are generated by oxidative bioactivation and blocking the sites that potentially undergo oxidative deactivation. Thus, the modification, including the incorporation of hydroxyl groups on the benzylic and the *para*-position, and the placement of two fluorine atoms on *para*-positions of the two lower aromatic rings, inhibited metabolic labile sites, and produced the drug Ezetimibe that expresses high potency in lower doses (right in Figure 1.7, shown in blue color).

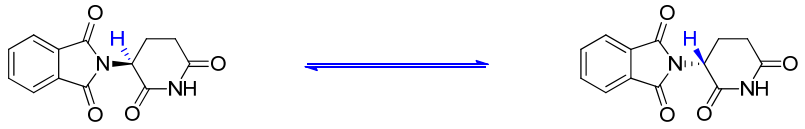
Figure 1.7. Blocking Metabolic Hot Spots Converts a Poor Lead to Drug Ezetimibe



Fluorine substitution can also reduce toxicity derived from the intrinsically chemical properties of therapeutic agents. For example, the drug thalidomide possesses an acidic hydrogen atom on α-carbon vicinal to a carbonyl group, which undergoes the *in vivo* epimerization (Figure 1.8A).[21a] Thus, the single enantiomer does not exist in the body, and thalidomide instead exists as a racemic mixture. However, only the (*R*)-enantiomer provides the desired sedative hypnotic activity, while the (*S*)-enantiomer produces the teratogenic side effects. For this drug, the replacement of the α-hydrogen atom by an F atom inhibits the *in vivo* epimerization (Figure 1.8B), and enables to access individual enantiomers for the biological evaluation of other potential pharmacological activities.[21b]

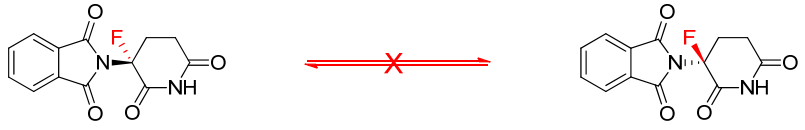
Figure 1.8. Fluorination Inhibits the Epimerization

A) *In Vivo* Epimerization of Thalidomide



(*S*)-thalidomide (*R*)-thalidomide

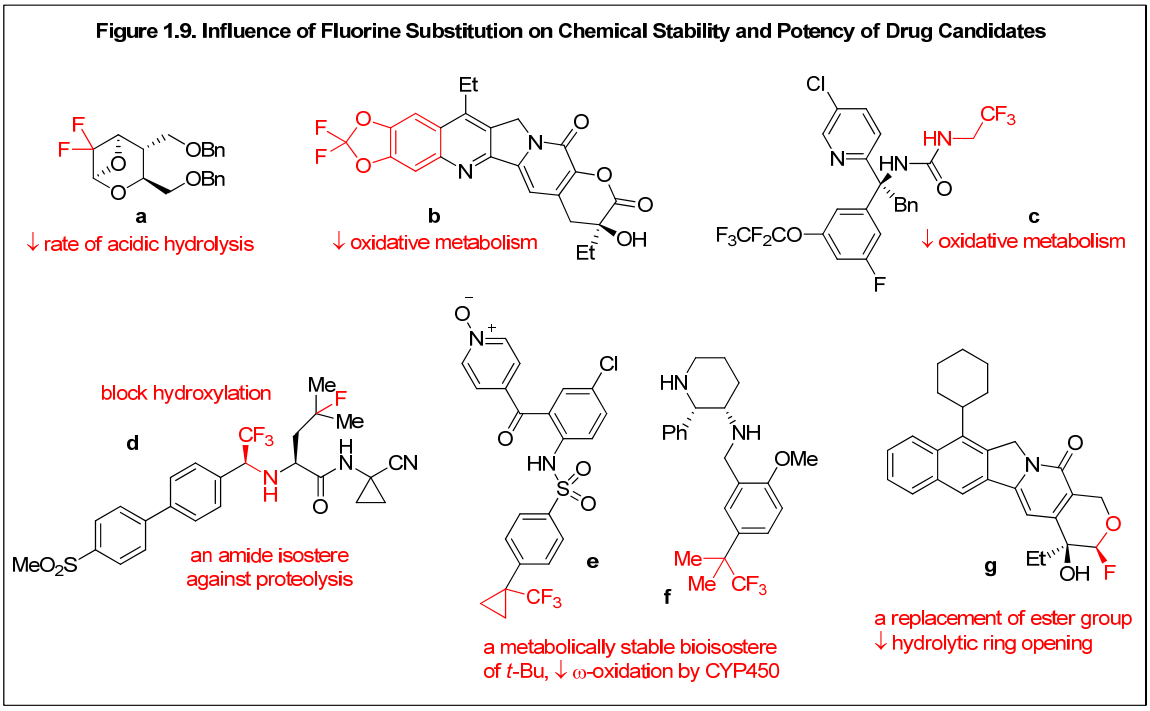
B) Fluorination Inhibits the Epimerization



(*R*)-fluorothalidomide (*S*)-fluorothalidomide

Other examples illustrating fluorination on chemically or metabolically labile sites to improve the stability of drug candidates are presented in Figure 1.9.[22] The difluorooxetane acetal moiety (**a**) is more stable than the parent acetal under neutral and acidic conditions, thus providing a potential application in designing drug molecules bearing labile acetal functionality.[22a] Moreover, the benzodioxole is an undesired motif on drug molecules, because it undergoes CYP450 oxidative metabolism to form a metabolite *ortho*-quinone, which can react with nucleophilic residues of other proteins, and cause the toxicity. However, incorporating two fluorine atoms into the methylene position of the benzodioxole inhibits the metabolic pathway and reduces the toxicity (**b**).[22b] Another example of fluorination to block metabolism is the replacement of the ethyl group on a nitrogen atom by a trifluoroethyl moiety (**c**), which retards oxidative dealkylation.[22c] Additionally, unique fluorinated motifs are utilized as metabolically stable isosteres of certain functional groups, such as the trifluoroethylamine moiety as a mimic of an amide bond (**d**),[22d] the trifluoromethylcyclopropyl and 1,1,1-trifluoro-2-methylpropyl as bioisosteres of a *tert*-butyl group (**e** and **f**),[22e,f] and the replacement of the C=O group by a C–F bond in acid-labile lactones (**g**).[22g]

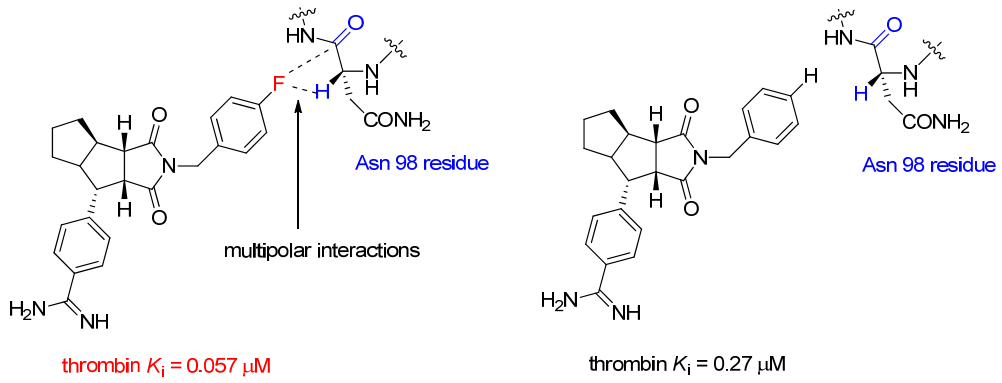
Figure 1.9. Influence of Fluorine Substitution on Chemical Stability and Potency of Drug Candidates



1.5 The Effect of F on Protein-Ligand Binding Interactions

Fluorine can play a direct role in modulating protein-ligand binding affinity. The strongly electronegative fluorine atom enables participation in polar interactions with the electropositive residues on the target protein and increase the binding affinity. An example representing such a direct effect of fluorine on binding affinity involved fluorinated thrombin inhibitors (Figure 1.10).[23a,b] The analog bearing a fluorine atom on aromatic C4 position of the *N*-benzyl moiety provided better potency (K_i = 0.057 μM) than the non-fluorinated counterpart (K_i = 0.27 μM). The X-ray crystal structure of the fluorinated ligand bound to thrombin revealed a close contact between the fluorine on aromatic C4 of the ligand and the amide moiety of the Asn 98 residue in the hydrophobic pocket of thrombin. In this region, the C–F bond represents an orthogonal arrangement to the C=O group of the amide moiety. Specifically, the fluorine atom formed non-covalently multipolar interactions with the partially positive charged C of the C=O group (C–F…C=O) and α-H adjacent to the C=O group (C–F…H–C_α), which enhanced the protein-ligand binding interactions, and the potency.

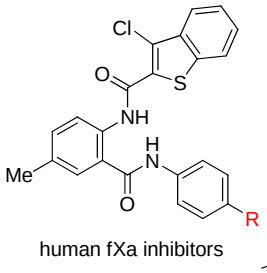
Figure 1.10. Fluorination Provides Multipolar Interactions and Enhances Potency



Additionally, fluorine substitution can directly enhance the binding affinity *via* lipophilic interactions. For example, in the series of human fXa inhibitors (Figure 1.11), the fluorinated analog (K_i = 11 nM, R= F) was more potent than non-fluorinated counterpart (K_i = 19 nM, R = H).[23c] Moreover, the potency (lower K_i values) increased with increasing sizes of the lipophilic R group on the analogues, then remarkably decreased with the analog bearing a CF_3 group. In this case, the improved potency

presumably derived from the increased non-specific (lipophilic) binding interactions between the fluorine atom and the fXa hydrophobic pocket. In the CF_3-substituted analog, the decreased potency was due to a steric clash between a large CF_3 group and the hydrophobic pocket.

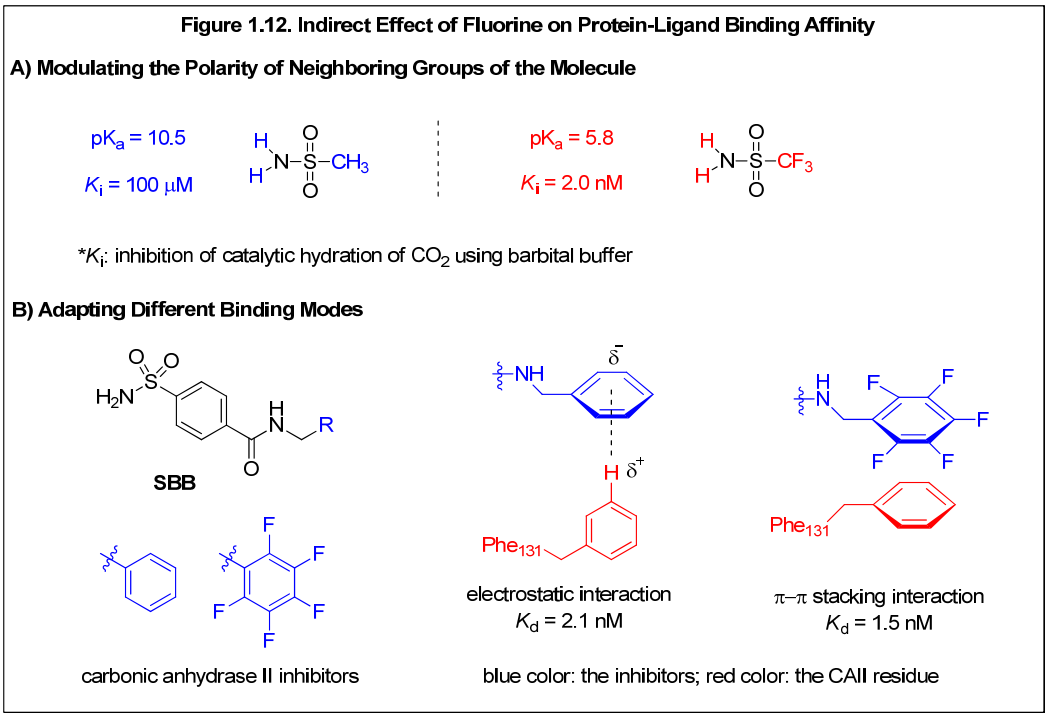
Figure 1.11. Fluorine Increases Lipophilic Interactions for the Hydrophobic Pocket of Human fXa



R	A value	fXa $K_{i,app}$ (nM)
H	0	19
F	0.15	11
Cl	0.43	0.32
Br	0.38	0.46
CF_3	2.1	> 5000

Fluorine can also interact indirectly with the protein by inductively modulating the polarity of neighboring functional groups, and affecting their binding to the target protein. An example representing the indirect effect of fluorine on the binding affinity involves carbonic anhydrase II (CAII) inhibitors (Figure 1.12A).[24a] The inhibitors usually possess a sulfonamide group that can ionize and bind to the zinc center of carbonic anhydrase II. The non-fluorinated inhibitor $CH_3SO_2NH_2$ is a weak acid (pK_a = 10.5) and cannot ionize and bind to the enzyme efficiently. However, the fluorinated inhibitor $CF_3SO_2NH_2$ is a stronger acid (pK_a = 5.8), and easily dissociated to form the anion that bound to the enzyme strongly. Thus, $CF_3SO_2NH_2$ revealed much higher potency (K_i = 2 nM) than $CH_3SO_2NH_2$ (K_i = 100 μM). The distinction between these two K_i values demonstrated the strong fluorine effect on modulating molecular polarity and binding affinity. Additionally, the indirect effect of fluorine can also in perturb binding affinity through the modification of the protein-ligand binding mode (Figure 1.12B). As in the case of carbonic anhydrase II (CAII) inhibitor **SBB**, the non-fluorinated analog binds to the enzyme differently from the fluorinated counterpart.[24b,c] The X-ray structure of the non-fluorinated analog bound to CAII represented an atom-to-face interaction, in which the electropositive hydrogen atom on the aromatic ring of the Phe-131 residue interacted with the ring current of the benzyl moiety of the inhibitor.[24b] In contrast, a face-to-face interaction dominated the fluorinated ligand to CAII binding. Specifically, the fluoroaromatic ring of the inhibitor interacted with the phenyl ring of the Phe-131 residue, and

demonstrated a π–π stacking interaction.[24b,c] These two binding modes provided slightly different binding affinities (CAII K_d = 2.1 nM for non-fluorinated inhibitor vs. CAII K_d = 1.5 nM for fluorinated inhibitor).

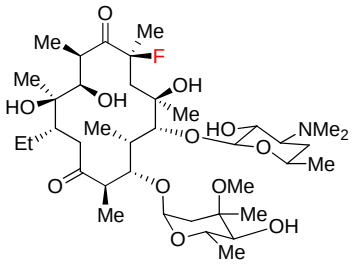


1.6 Fluorine as a Key Component of Drugs

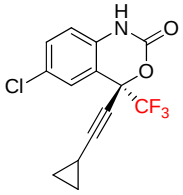
Because of the beneficial influences of fluorine on physicochemical properties, lipophilicity, conformational modulation, metabolic stability, and binding affinity, fluorine atoms or fluorinated groups represent key structural components of therapeutic agents. Many drugs on the market contain fluorinated motifs, including but not limited to single fluorine atom, difluoromethylene CF_2 unit, trifluoromethyl CF_3 group. Moreover, these fluorine-containing drugs range from the derivatives of natural products to small molecules, and comprise a variety of pharmacological activities as shown in Figure 1.13.[4] For example, flurithromycin is a fluorinated analog of the antibiotic erythromycin. Erythromycin undergoes an acid-induced degradation to generate the ketal side product on the C9 position.[25a] However, Fluorination on the C8 position of erythromycin disfavors the degradative pathway and inhibits the formation of the ketal side product.[25b] Thus, flurithromycin displays higher stability under acidic conditions than erythromycin.[25b] Moreover, Efavirenz is an antiretroviral drug that acts at an allosteric site of NNRT (non-nucleoside

reverse transcriptase), and inhibits the synthesis of viral DNA. The presence of a strong electron-withdrawing CF_3 group lowers pK_a, and increases the ionization of the N–H bond of the cyclic carbamate, which improves the solubility of the drug.[25c] In other drugs, fluorinated groups serve different purposes, such as conformational modification (Fluoxetine),[25d] enhanced potency and selectivity (Celecoxib),[25e] and the modulation of pharmacological activity (Faslodex),[25f] while some of them bear fluorine for unclear reasons.

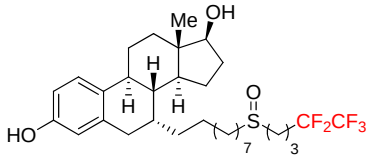
Figure 1.13. Representative Examples of Fluorine-Containing Drugs Approved



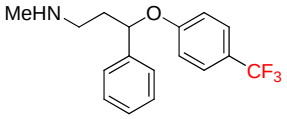
Flurithromycin
anti-bacterial drug



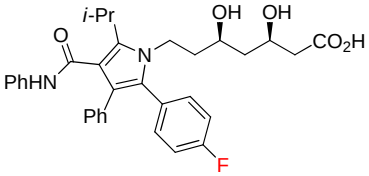
Efavirenz
anti-HIV drug



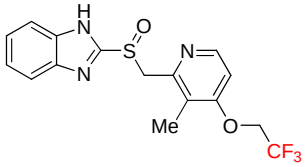
Faslodex
anti-cancer drug



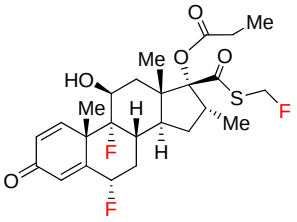
Fluoxetine
anti-depressant drug



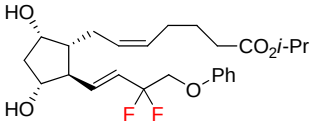
Lipitor
cholesterol-lowering drug



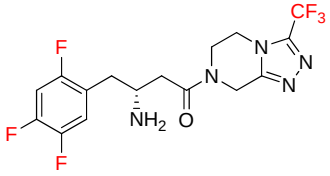
Lansoprazole
gastric acid-inhibiting drug



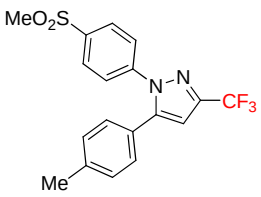
fluticasone propionate
anti-inflammatory drug



Travoprost
glaucoma drug



Sitagliptin
anti-diabetic drug

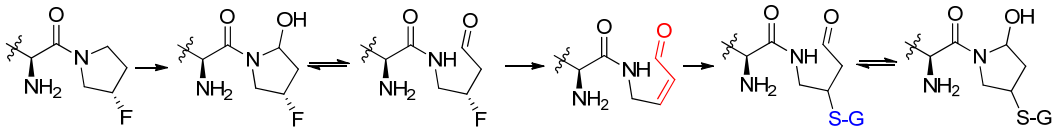


Celecoxib
nonsteroidal anti-inflammatory drug

1.7 Conclusion

Fluorine atoms or fluorinated groups are popular structural motifs in drug design because of unique features transmitted by fluorine. However, fluorine atoms need to be installed on the appropriate positions to achieve maximum beneficial effects. Incorporating fluorine into the improper position can result in reverse effects, as observed in 3-fluoropyrrolidine.[26] In this case, the 3-fluoropyrrolidine analog undergoes metabolic activation followed by elimination of HF to generate the Michael acceptor, which reacts with the protein to form covalent adducts, and causes the toxicity (Figure 1.14).

Figure 1.14. Fluorination on C3 Position of Pyrrolidine Generates the Reactive Metabolite



In order to place fluorine atoms on the correct position, a fluorine scan is a common method for SAR (structure-activity relationship) studies unless key metabolic hot spots are already known. Fluorine scans require a series of analogues with fluorine or fluorinated groups on different positions of the molecules for the bioassays. Thus, the strategies to synthesize the designed fluorinated molecules are important. However, few fluorinated molecules are biosynthesized by enzymes, because 1) high oxidation potential of fluorine prevents the formation of the hypohalous species, which are key intermediates involved in the enzymatic halogenation; and 2) high hydration energy makes fluoride a poor nucleophile, which cannot attack epoxides generated in biological systems.[27] This means the introduction of fluorine into molecules exclusively relies on chemically synthetic pathways. Thus, chemical methodologies to access fluorinated building blocks are necessary, and they benefit the development of fluorinated drugs, and biological probes.

1.8 References for Chapter 1

[1] Fried, J.; Sabo, E. F. "9α-Fluoro Derivatives of Cortisone and Hydrocortisone" *J. Am. Chem. Soc*. **1954**, *76*, 1455–1456.

[2] (a) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. "Fluorinated Pyrimidines, A New Class of Tumor-Inhibitory Compounds" *Nature* **1957**, *179*, 663–666. (b) Longley, D. B.; Harkin, D. P.; Johnston, P. G. "5-Fluorouracil: Mechanisms of Action and Clinical Strategies" *Nat. Rev. Cancer* **2003**, *3*, 330–338.

[3] Hagmann, W. K. "The Many Roles for Fluorine in Medicinal Chemistry" *J. Med. Chem*. **2008**, *51*, 4359–4369.

[4] Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; 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*, 2432–2506.

[5] (a) Chambers, R. D. "*Fluorine in Organic Chemistry*" Blackwell, Oxford, **2000**.

[6] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. "Fluorine in Medicinal Chemistry" *Chem. Soc. Rev*. **2008**, *37*, 320–330. (b) 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*, 8315–8359.

[7] Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. "Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities" *ChemMedChem* **2007**, *2*, 1100–1115.

[8] Rowley, M.; Hallett, D. J.; Goodacre, S.; Moyes, C.; Crawforth, J.; Sparey, T. J.; Patel, S.; Marwood, R.; Patel, S.; Thomas, S.; Hitzel, L.; O'Connor, D.; Szeto, N.; Castro, J. L.; Hutson, P. H.; Macleod, A. M. "3-(4-Fluoropiperidin-3-yl)-2-phenylindoles as High Affinity, Selective, and Orally Bioavailable h5-HT_{2A} Receptor Antagonists" *J. Med. Chem*. **2001**, *44*, 1603–1614.

[9] (a) Kokuryo, Y.; Kawata, K.; Nakatani, T.; Kugimiya, A.; Tamura, Y.; Kawada, K.; Matsumoto, M.; Suzuki, R.; Kuwabara, K.; Hori, Y.; Ohtani, M. "Synthesis and Evaluation of Novel Fluorinated Methotrexate Derivatives for Application to Rheumatoid Arthritis Treatment" *J. Med. Chem*. **1997**, *40*, 3280–3291. (b) Qiu, J.; Stevenson, S. H.; O'Beirne, M. J.; Silverman, R. B. "2,6-Difluorophenol as a Bioisostere of a Carboxylic Acid: Bioisosteric Analogs of γ-Aminobutyric Acid" *J. Med. Chem*. **1999**, *42*, 329–332.

[10] Fagerholm, U. The role of permeability in drug ADME/PK, interactions and toxicity, and the permeability-based classification system (PCS). *Burger's Medicianl Chemistry and Drug Discovery*, 7th ed.; Abraham, D. J.; Rotella, D. P., Eds.; Wiley: New York, **2010**; pp 367–380.

[11] (a) 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*, 637–643. (b) Smart, B. E. "Fluorine Substituent Effects (on Bioactivity)" *J. Fluorine Chem*. **2001**, *109*, 3–11. (c) 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.

[12] (a) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. "A DFT Study on the Origin of the Fluorine *Gauche* Effect in Substituted Fluoroethanes" *Tetrahedron* **2010**, *66*, 2196–2202. (b) Zimmer, L. E.; Sparr, C.; Gilmour, R. "Fluorine Conformational Effects in Organocatalysis: An Emerging Strategy for Molecular Design" *Angew. Chem. Int. Ed*. **2011**, *50*, 11860–11871.

[13] Myers, A. G.; Barbay, J. K.; Zhong, B. "Asymmetric Synthesis of Chiral Organofluorine Compounds: Use of Nonracemic Fluoroiodoacetic Acid as a Practical Electrophile and Its Application to the Synthesis of Monofluoro Hydroxyethylene Dipeptide Isosteres within a Novel Series of HIV Protease Inhibitors" *J. Am. Chem. Soc*. **2001**, *123*, 7207–7219.

[14] (a) Peddie, V.; Butcher, R. J.; Robinson, W. T.; Wilce, M. C. J.; Traore, D. A. K.; Abell, A. D. "Synthesis and Conformation of Fluorinated β-Peptidic Compounds" *Chem. Eur. J*. **2012**, *18*, 6655–6662.

(b) O'Hagan, D.; Bilton, C.; Howard, J. A. K.; Knight, L.; Tozer, D. J. "The Preferred Conformation of *N*-β-Fluoroethyl Amides. Observation of the Fluorine Amide *Gauche* Effect" *J. Chem. Soc., Perkin Trans. 2*, **2000**, 605–607. (c) Winkler, M.; Moraux, T.; Khairy, H. A.; Scott, R. H.; Slawin, A. M. Z.; O'Hagan, D. "Synthesis and Vanilloid Receptor (TRPV1) Activity of the Enantiomers of α-Fluorinated Capsaicin" *ChemBioChem* **2009**, *10*, 823–828.

[15] 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.; Willams, T. M. "Identification of Potent, Highly Constrained CGRP Receptor Antagonists" *Bioorg. Med. Chem. Lett*. **2010**, *20*, 2572–2576.

[16] (a) Hehre, W. J.; Radom, L.; Pople, J. A. "Molecular Orbital Theory of the Electronic Structure of Organic Compounds. XII. Conformations, Stabilities, and Charge Distributions in Monosubstituted Benzenes" *J. Am. Chem. Soc*. **1972**, *94*, 1496–1504. (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*, No. 13, No pp. (c) Marrec, O.; Billard, T.; Vors, J.-P.; Pazenok, S.; Langlois, B. R. "A Deeper Insight into Direct Trifluoromethoxylation with Trifluoromethyl Triflate" *J. Fluorine Chem*. **2010**, *131*, 200–207. (d) 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*, 715–726. (e) Horne, D. B.; Bartberger, M. D.; Kaller, M. R.; Monenschein, H.; Zhong, W.; Hitchcock, S. A. "Synthesis and Conformational Analysis of α,α-Difluoroalkyl Heteroaryl Ethers" *Tetrahedron Lett.* **2009**, *50*, 5452–5455.

[17] Massa, M. A.; Spangler, D. P.; Durley, R. C.; Hickory, B. S.; Connolly, D. T.; Witherbee, B. J.; Smith, M. E.; Sikorski, J. A. "Novel Heteroaryl Replacements of Aromatic 3-Tetrafluoroethoxy Substituents in Trifluoro-3-(tertiary amino)-2-propanols as Potent Inhibitors of Cholesteryl Ester Transfer Protein" *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1625–1628.

[18] Smith, D. H.; van de Waterbeemd, H.; Walker, D. K. *Pharmacokinetics and Metabolism in Drug Design, Methods and Principles in Medicinal Chemistry*, Wiley-VCH, Weinheim, **2001**, *Vol. 13*.

[19] (a) Cho, M. J.; Allen, M. A. "Chemical Stability of Prostacyclin (PGI_2) in Aqueous Solutions" *Prostaglandins*, **1978**, *15*, 943–954. (b) Bannai, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. "Prostaglandin Chemistry. XX. Synthesis of Chemically Stable Prostacyclin Analogs" *Tetrahedron* **1983**, *39*, 3807–3819. (c) Chang, C.-S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. "7,7-Difluoroprostacyclin Derivative, AFP-07, a Highly Selective and Potent Agonist for the Prostacyclin Receptor" *Prostaglandins*, **1997**, *53*, 83–90.

[20] (a) van Heek, M.; France, C. F.; Compton, D. S.; McLeod, R. L.; Yumibe, N. P.; Alton, K. B.; Sybertz, E. J.; Davis, H. R., Jr. "*In Vivo* Metabolism-Based Discovery of a Potent Cholesterol Absorption Inhibitor, SCH58235, in the Rat and Rhesus Monkey through the Identification of the Active Metabolites of SCH48461" *J. Pharmacol. Exp. Ther*. **1997**, *283*, 157–163. (b) Clader, J. W. "The Discovery of Ezetimibe: A View from outside the Receptor" *J. Med. Chem*. **2004**, *47*, 1–9.

[21] (a) Eriksson, T.; Bjöerkman, S.; Roth, B.; Fyge, A.; Höeglund, P. "Stereospecific Determination, Chiral Inversion *in vitro* and Pharmacokinetics in Humans of the Enantiomers of Thalidomide" *Chirality* **1995**, *7*, 44–52. (b) Takeuchi, Y.; Shiragami, T.; Kimura, K.; Suzuki, E.; Shibata, N. "(*R*)- and (*S*)-3-Fluorothalidomides: Isosteric Analogs of Thalidomide" *Org. Lett*. **1999**, *1*, 1571–1573.

[22] (a) Fried, J.; John, V.; Szwedo, M. J., Jr.; Chen, C. K.; O'Yang, C.; Morinelli, T. A.; Okwu, A. K.; Halushka, P. V. "Synthesis of 10,10-Difluorothromboxane A_2, a Potent and Chemically Stable Thromboxane Agonist" *J. Am. Chem. Soc*. **1989**, *111*, 4510–4511. (b) Rose, W. C.; Marathe, P. H.; Jang, G. R.; Monticello, T. M.; Balasubramanian, B. N.; Long, B.; Fairchild, C. R.; Wall, M. E.; Wani, M. C. "Novel Fluoro-Substituted Camptothecins: *In Vivo* Antitumor Activity, Reduced Gastrointestinal Toxicity and Pharmacokinetic Characterization" *Cancer Chemother. Pharmacol*. **2006**, *58*, 73–85. (c) Miller, M. M.; Liu, Y.; Jiang, J.; Johnson, J. A.; Kamau, M.; Nirschl, D. S.; Wang, Y.; Harikrishnan, L.; Taylor, D.

S.; Chen, A. Y. A.; Yin, X.; Seethaia, R.; Peterson, T. L.; Zvyaga, T.; Zhang, J.; Huang, C. S.; Wexler, R. R.; Poss, M. A.; Michael Lawrence, R.; Adam, L. P.; Salvati, M. E. "Identification of a Potent and Metabolically Stable Series of Fluorinated Diphenylpyridylethanamine-Based Cholesteryl Ester Transfer Protein Inhibitors" *Bioorg. Med. Chem. Lett*. **2012**, *22*, 6503–6508. (d) Gauthier, J. Y.; Chauret, N.; Cromlish, W.; Desmarais, S.; Duong, L. T.; Falgueyret, J.-P.; Kimmel, D. B.; Lamontagne, S.; Léger, S.; LeRiche, T.; Li, C. S.; Massé, F.; McKay, D. J.; Nicoll-Griffith, D. A.; Oballa, R. M.; Palmer, J. T.; David Percival, M.; Riendeau, D.; Robichaud, J.; Rodan, G. A.; Rodan, S. B.; Seto, C.; Thérien, M.; Truong, V.-L.; Venuti, M. C.; Wesolowski, G.; Young, R. N.; Zamboni, R.; Cameron Black, W. "The Discovery of Odanacatib (MK-0822), a Selective Inhibitor of Cathepsin K" *Bioorg. Med. Chem. Lett*. **2008**, *18*, 923–928. (e) Tanaka, H.; Shishido, Y. "Synthesis of Aromatic Compounds Containing a 1,1-Dialkyl-2-trifluoromethyl Group, a Bioisostere of the *tert*-Alkyl Moiety" *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6079–6085. (f) Westphal, M. V.; Wolfstädter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. "Evaluation of *tert*-Butyl Isosteres: Case Studies of Physicochemical and Pharmacokinetic Properties, Efficacies, and Activities" *ChemMedChem* **2015**, *10*, 461–469. (g) Miao, Z.; Zhu, L.; Dong, G.; Zhuang, C.; Wu, Y.; Wang, S.; Guo, Z.; Liu, Y.; Wu, S.; Zhu, S.; Fang, K.; Yao, J.; Li, J.; Sheng, C.; Zhang, W. "A New Strategy to Improve the Metabolic Stability of Lactone: Discovery of (20*S*,21*S*)-21-Fluorocamptothecins as Novel, Hydrolytically Stable Topoisomerase I Inhibitors" *J. Med. Chem*. **2013**, *56*, 7902–7910.

[23] (a) Olsen, J. A.; Banner, D. W.; Seiler, P.; Sander, U. O.; D'Arcy, A.; Stihle, M.; Müeller, 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*. **2003**, *42*, 2507–2511. (b) Hof, F.; Scofield, D. M.; Schweizer, W. B.; Diederich, F. "A Weak Attractive Interaction between Organic Fluorine and an Amide Group" *Angew. Chem. Int. Ed*. **2004**, *43*, 5056–5059. (c) Chou, Y.-L.; Davey, D. D.; Eagen, K. A.; Griedel, B. D.; Karanjawala, R.; Phillips, G. B.; Sacchi, K. L.; Shaw, K. J.; Wu, S. C.; Lentz, D.; Liang, A. M.; Trinh, L.; Morrissey, M. M.; Kochanny, M. J. "Structure-Activity Relationships of Substituted Benzothiophene-Anthranilamide Factor Xa Inhibitors" *Bioorg. Med. Chem. Lett*. **2003**, *13*, 507–511.

[24] (a) Maren, T. H.; Conroy, C. W. "A New Class of Carbonic Anhydrase Inhibitor" *J. Biol. Chem*. **1993**, *268*, 26233–26239. (b) Kim, C.-Y.; Chang, J. S.; Doyon, J. B.; Baird, T. T., Jr.; Fierke, C. A.; Jain, A.; Christianson, D. W. "Contribution of Fluorine to Protein-Ligand Affinity in the Binding of Fluoroaromatic Inhibitors to Carbonic Anhydrase II" *J. Am. Chem. Soc*. **2000**, *122*, 12125–12134. (c) Doyon, J. B.; Jain, A. "The Pattern of Fluorine Substitution Affects Binding Affinity in a Small Library of Fluoroaromatic Inhibitors for Carbonic Anhydrase" *Org. Lett*. **1999**, *1*, 183–185.

[25] (a) Mordi, M. N.; Pelta, M. D.; Boote, V.; Morris, G. A.; Barber, J. "Acid-Catalyzed Degradation of Clarithromycin and Erythromycin B: A Comparative Study Using NMR Spectroscopy" *J. Med. Chem*. **2000**, *43*, 467–474. (b) Fera, M. T.; Giannone, M.; Pallio, S.; Tortora, A.; Blandino, G.; Carbone, M. "Antimicrobial Activity and Postantibiotic Effect of Flurithromycin against *Helicobacter Pylori* Strains" *Int. J. Antimicrob. Agents*. **2001**, *17*, 151–154. (c) Rabel, S. R.; Patel, M.; Sun, S.; Maurin, M. B. "Electronic and Resonance Effects on the Ionization of Structural Analogues of Efavirenz" *PPAS PharmSci* **2001**, *3*, E28. (d) Roman, D. L.; Walline, C. C.; Rodriguez, G. J.; Barker, E. L. "Interactions of Antidepressants with the Serotonin Transporter: A Contemporary Molecular Analysis" *Eur. J. Pharmacol*. **2003**, *479*, 53–63. (e) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib)" *J. Med. Chem*. **1997**, *40*, 1347–1365. (f) Robertson, J. F. R.; Come, S. E.; Jones, S. E.; Beex, L.; Kaufmann, M.; Makris, A.; Nortier, J. W. R.; Possinger, K.; Rutqvist, L.-E. "Endocrine Treatment Options for Advanced Breast Cancer-the Role of Fulvestrant" *Eur. J. Cancer* **2005**, *41*, 346–356.

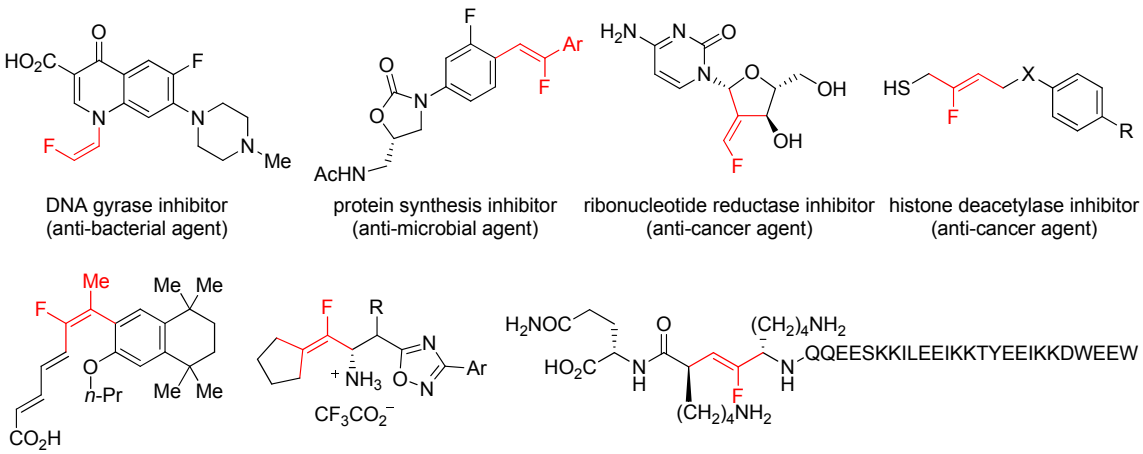
[26] Xu, S.; Zhu, B.; Teffera, Y.; Pan, D. E.; Caldwell, C. G.; Doss, G.; Stearns, R. A.; Evans, D. C.; Beconi, M. G. "Metabolic Activation of Fluoropyrrolidine Dipeptidyl Peptidase-IV Inhibitors by Rat Liver Microsomes" *Drug Metab. Dispos*. **2005**, *33*, 121–130.
[27] O'Hagan, D.; Deng, H. "Enzymatic Fluorination and Biotechnological Developments of the Fluorinase" *Chem. Rev*. **2015**, *115*, 634–649.

Chapter 2. Preparation of Peptidomimetic Fluoroalkenes *via* a Shapiro Reaction

2.1 Introduction to Fluoroalkenes

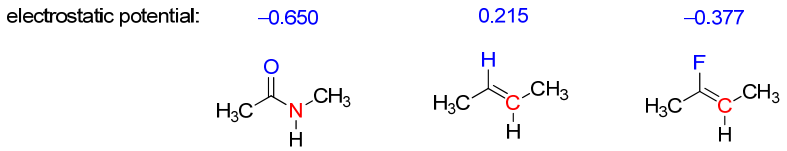
Fluoroalkenes represent an underappreciated functional group with applications in medicinal, synthetic, and materials chemistry. In medicinal chemistry, the fluoroalkene motif is broadly found in a variety of bioactive compounds with distinct pharmacological profiles, including antimicrobial, anti-cancer,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

Figure 2.1. Representative Examples of Bioactive Fluoroalkene-Containing Molecules



Moreover, the fluoroalkene group serves as an isopolar and isosteric mimic of an amide (Figure 2.2), and provides an alternative in the design of peptidomimetic drugs.[2] First, amide molecules and fluoroalkenes have similar electrostatic potential maps, which mean a similar charge distribution between the two molecules. Second, the dipole moment of fluoroalkenes is closer to that of amides, indicating fluoroalkenes and amides have similar molecular polarity and geometry. Third, fluorine on fluoroalkenes has an atomic size that is similar to the size of oxygen of an amide bond. Additionally, because of the electronegative similarity between the oxygen and fluorine atoms, fluorinated alkenes preserve the dipolar nature of an amide bond, and may participate in weak H-bond or polar interactions with the receptors compared to nonpolar and H-bond lacking olefins.[2]

Figure 2.2. Fluoroalkenes as Isosteric and Isopolar Mimic of Amide Bonds

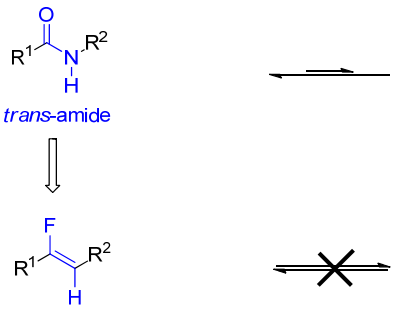


However, amide bonds and fluoroalkenes have some distinct biophysical properties. Compared to amides, fluoroalkenes possess decreased H-bond donating and accepting abilities,[3] and they can pass through the lipid bilayers with less expenditure of the desolvation energy.[4] Thus, the strategic incorporation of a fluoroalkene into a biological probe can increase lipophilicity and membrane permeability.[4] Additionally, fluorinated peptidomimetics are not subject to hydrolysis by proteases,[5a] and the electron-withdrawing effect of fluorine can prevent or slow chemical decomposition of a chemically labile molecule imposed by adjacent reactive groups in the structure.[5b,c] Therefore, the incorporation of this fluorinated group can improve the metabolic and chemical stability of a peptide.[5]

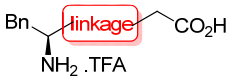
Additionally, amide bonds can exist in the equilibrium of *cis*- and *trans*-isomers; however, fluoroalkenes do not undergo the isomerization and are conformationally locked (Figure 2.3A). Thus, fluoroalkenes can serve as probes for conducting conformational analyses of amides by selective preparation of *E*- and *Z*-fluoroalkene isomers (Figure 2.3B).[6]

Figure 2.3. *E*- or *Z*-Fluoroalkenes as Probes for Conducting Conformational Analyses of Amides

A) Stereoselective Control of *E*- or *Z*-Fluoroalkenes



B) Various Isosteres to Probe Structural Requiremens of the PEPT1 Enzyme[5]



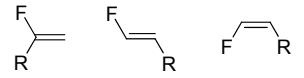
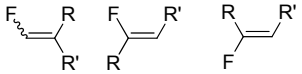
linkage	K_i (mM)
–CO-NH–	0.205
–Ψ[(*Z*)-CH=CH]–	> 10.0
–Ψ[(*Z*)-CF=CH]–	1.34
–Ψ[(*E*)-CH=CH]–	0.853
–Ψ[(*E*)-CF=CH]–	> 10.0

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

2.2 Literature Review to Access Fluoroalkenes

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

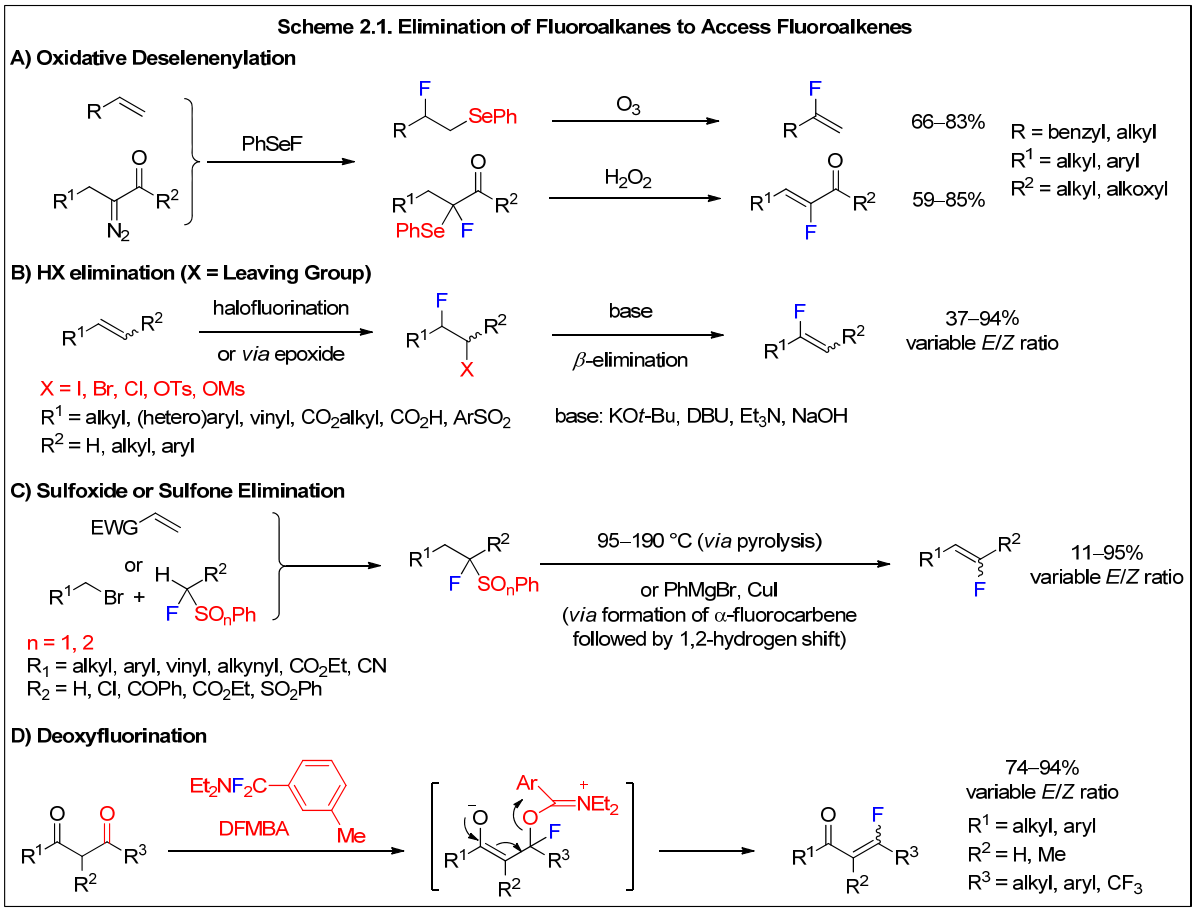
Table 2.1. Classification of Fluoroalkenes and Synthetic Methods

substitution pattern	structure	common synthetic methods
disubstitution	 α-fluoro β-*E*-fluoro β-*Z*-fluoro	addition-elimination electrophilic fluorination transition metal-catalyzed coupling reactions
trisubstitution	 *Z*-fluoro *E*-fluoro	addition-elimination olefination reactions transition metal-catalyzed coupling reactions reactions of allylic *gem*-difluorides
tetrasubstitution		olefination reactions transition metal-catalyzed coupling reactions

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

2.2.1 Elimination of Fluoroalkanes

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

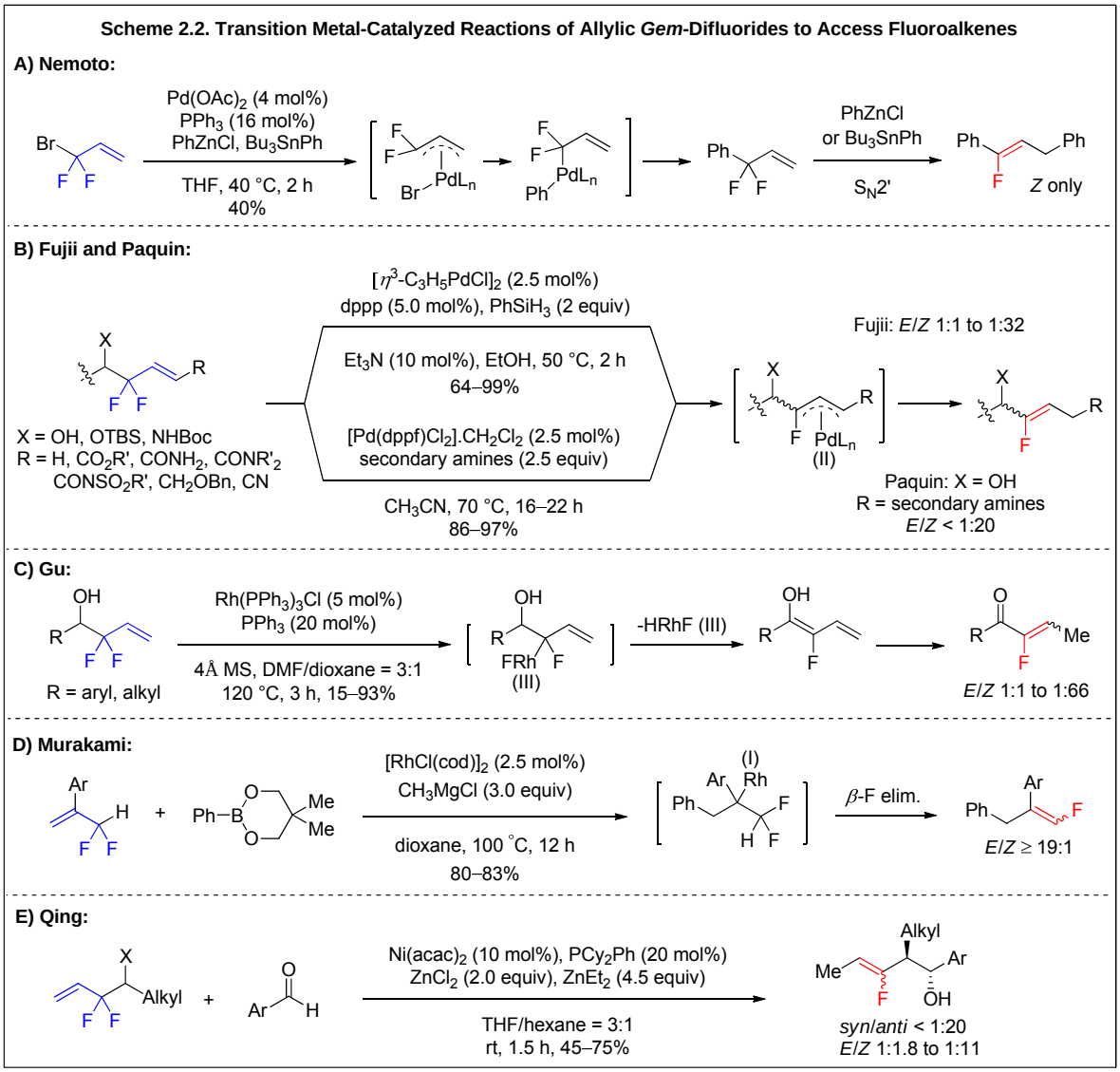


2.2.2 Allylic Gem-Difluorides Oriented Methods

The allylic *gem*-difluoride oriented strategy utilizes pre-functionalized allylic *gem*-difluorides as starting materials to access fluoroalkene derivatives *via* 1) transition metal-catalyzed reactions; 2) transition metal-free reductive defluorination; or 3) nucleophilic defluorination. First, the Nemoto lab reported substitution reactions of allylic *gem*-difluorides with phenylzinc chloride or tributylphenyl tin *via* a *gem*-difluoro Pd-π-allyl intermediate (Scheme 2.2A).[12a] Subsequently, the Fujii and Paquin groups applied allylic C–F bond activation to generate a similar fluorinated Pd-π-allyl complex, which reacts with hydrides and *N*-based nucleophiles to access fluoroalkenes (Scheme 2.2B).[12b,c] In addition to palladium catalysts, other transition metals have been explored for coupling reactions. For example, the Gu lab used rhodium (I) to couple α-(difluoromethyl)styrenes with arylboronic esters *via* 1,2-addition of phenylrhodium(I) species followed by β-fluoride elimination to generate fluoroalkenes (Scheme 2.2C),[12d]

and a similar rhodium(I) catalyst has been employed in synthesizing ketone-substituted fluoroalkenes by a different mechanism in the Murakami group (Scheme 2.2D).[12e] In 2012, the Qing lab demonstrated a regio- and diastereoselective nickel-catalyzed reductive coupling strategy of dienes and aldehydes to access fluoroolefinic alcohols (Scheme 2.2E).[12f]

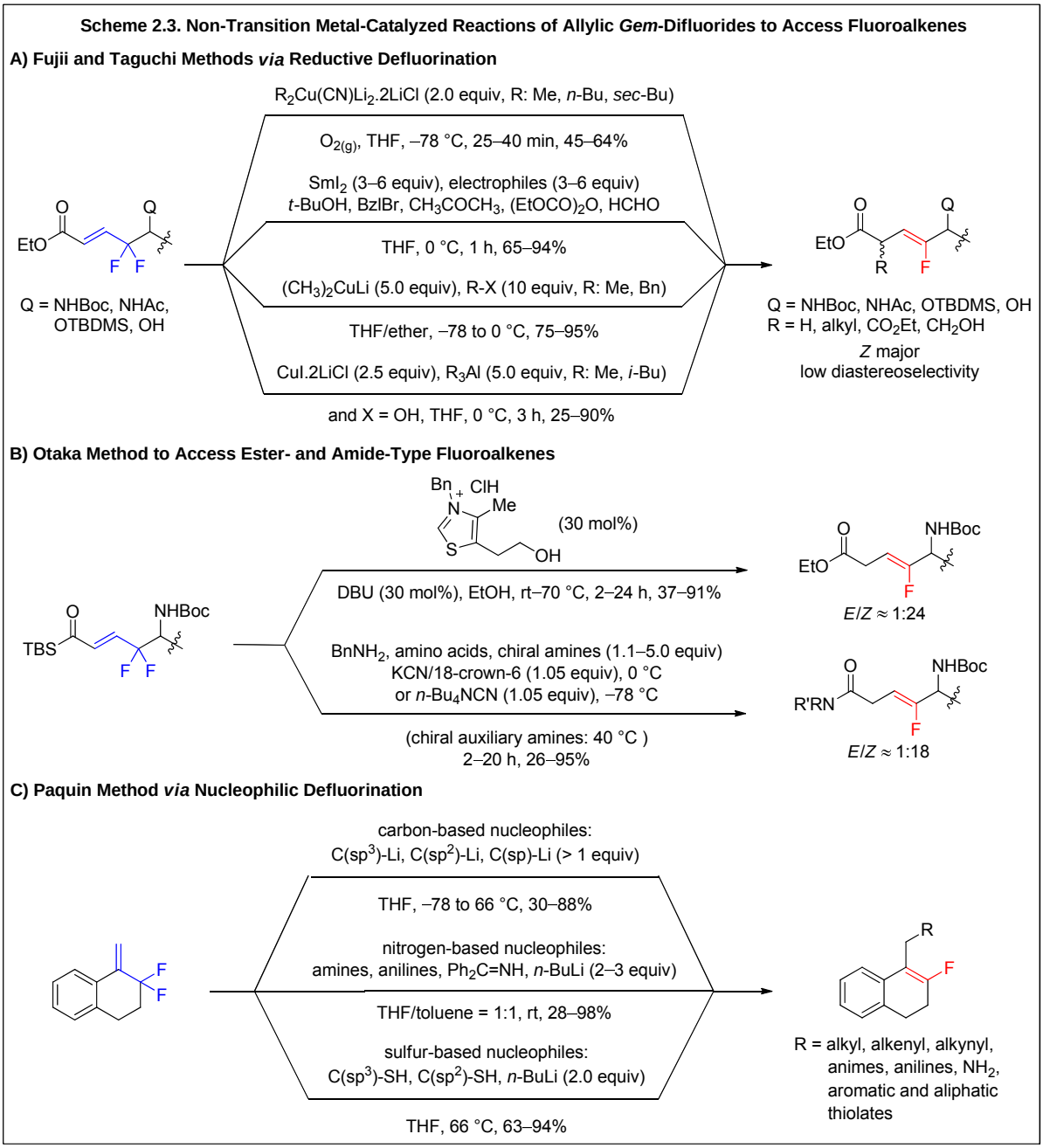
Scheme 2.2. Transition Metal-Catalyzed Reactions of Allylic *Gem*-Difluorides to Access Fluoroalkenes



The Fujii and Taguchi labs utilized reductive defluorination of δ-amino-γ,γ-difluoro-α,β-enoates for accessing α-alkyl-γ-fluoro-β,γ-enoates. These methods involved Me_2CuLi- and SmI_2-mediated single electron transfer followed by electrophilic alkylation on the α position and Cu(I)-mediated alkyl transfer with trialkylaluminum to generate fluoroalkene products, respectively (Scheme 2.3A).[13a–c] Later, the

Otaka group extended this strategy to the reactions of γ,γ-difluoro-α,β-enoylsilanes with *N*-heterocyclic carbenes and cyanide ions as nucleophiles to generate ester-type and amide-type fluoroalkenes *via* a Brook rearrangement (Scheme 2.3B).[13d,e] The Paquin lab reported a series of S_N2' reactions of allylic *gem*-difluorides with *C*-, *N*-, and *S*-based nucleophiles for the construction of C–C, C–N, and C–S bonds, which enabled to access heteroatom-containing fluoroalkene products (Scheme 2.3C).[13f]

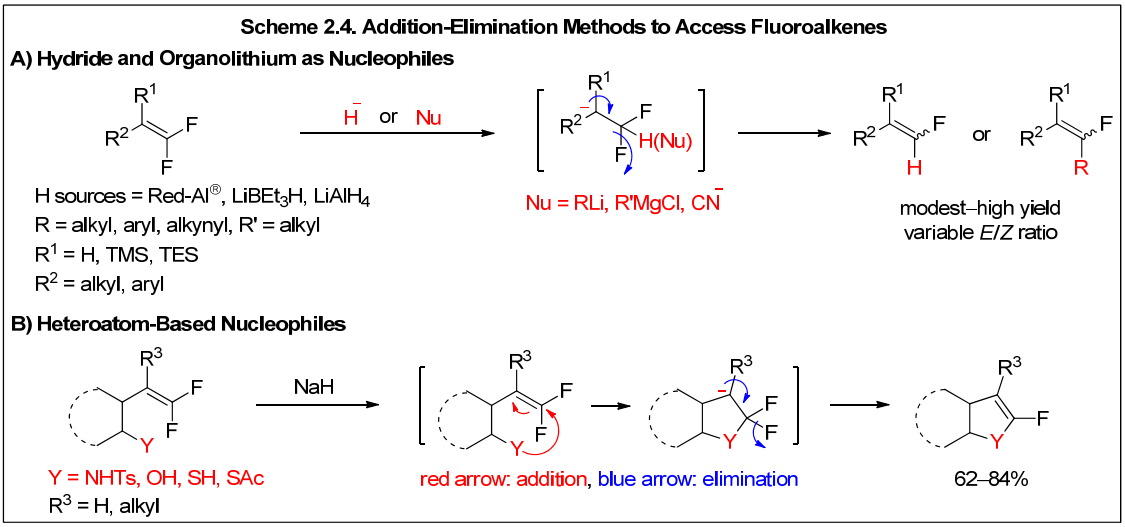
Scheme 2.3. Non-Transition Metal-Catalyzed Reactions of Allylic *Gem*-Difluorides to Access Fluoroalkenes



2.2.3 Addition-Elimination of Gem-Difluoroalkenes

Nucleophilic addition of *gem*-difluoroalkenes (CF_2 unit on the vinylic position) followed by elimination of a fluoride anion provides a common approach to generate fluoroalkenes. For these transformations, intermolecular reactions required the use of hydrides, and carbon-based nucleophiles (Scheme 2.4A),[14a–g] while intramolecular additions were limited to heteroatom-based nucleophiles and formed five-membered heterocycles (Scheme 2.4B).[14h]

Scheme 2.4. Addition-Elimination Methods to Access Fluoroalkenes

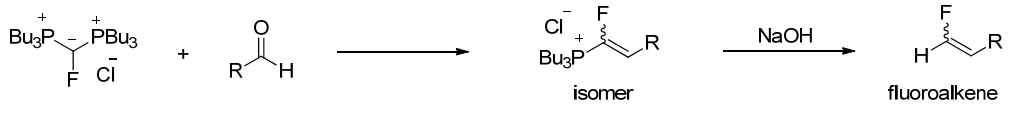


2.2.4 Olefination Reactions

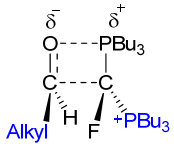
The reactions of fluorinated phosphorus ylides with carbonyl compounds represent conventional methods for accessing tri- and tetra-substituted functionalized fluoroalkenes, which enable further modifications to generate complex fluoroolefin-containing molecules. However, the selectivity for *E*- and *Z*-isomers of olefination reactions is difficult to predict, and depends on many factors, including reaction conditions, ylides, and substituents of carbonyl groups. To ameliorate the *E*/*Z* selectivity, several subtypes of olefination reactions were developed, including Wittig, Horner-Wadsworth-Emmons (HWE), Julia-Kocienski, and Peterson olefinations, each of which bears different auxiliary groups on the ylides. In 1985, the Burton lab reported Wittig reactions of a stabilized ylide $CF(PBu_3)_2Cl$ with aldehydes, and the stereoselectivity was controlled by structure of the aldehydes with aliphatic substrates providing the *E*-isomer and aromatic substrates forming the *Z*-isomer. The formation of less common *Z*-isomers in the

Wittig reaction was attributed to two possible reasons: 1) through-space cation-π attraction between the phosphonium center of ylides and the aromatic ring of aldehydes or 2) electron-electron repulsion between the electronegative fluorine atom and π-electrons in an aromatic aldehyde (Scheme 2.5).[15]

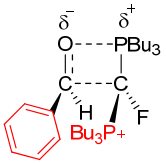
Scheme 2.5. Wittig Reactions to Access Stereoselective Fluoroalkenes by the Burton Lab



R	*E*/*Z* (isomer)	*E*/*Z* (fluoroalkene)	yield (%)
$CH_3(CH_2)_5$	97:3	0:100	51
C_6H_{11}	100:0	0:100	50
C_6H_5	13:87	87:13	61
4-$OMeC_6H_4$	17:83	83:17	51
4-ClC_6H_4	21:79	75:25	60
3-$CF_3C_6H_4$	25:75	75:25	57
2-MeC_6H_4	0:100	100:0	50



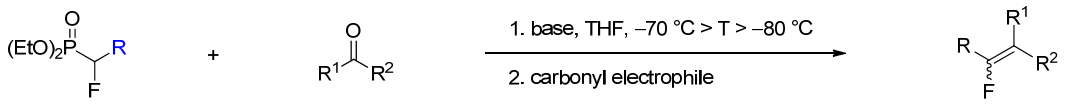
steric repulsion
TS for aliphatic aldehydes
E-isomer
Z-fluoroalkene



cation-π interaction
TS for aromatic aldehydes
Z-isomer
E-fluoroalkene

In modified HWE reactions, the Penne group applied the fluorinated phosphonate $(EtO)_2P(O)CHFCO_2Me$ to HWE reactions, and the selectivity was influenced by the reaction temperature, with *E*-fluoroalkenes dominating at –78 °C.[16a] Additionally, many research groups developed similar HWE reactions using sulfone-,[16b] nitrile-,[16c] phenyl-,[16d] and alkyne[16e]-substituted fluorinated phosphonates for accessing a variety of functionalized fluoroalkenes in good yield with low to modest stereoselectivity (Scheme 2.6).

Scheme 2.6. Horner-Wadsworth-Emmons (HWE) Reactions to Access Functionalized Fluoroalkenes

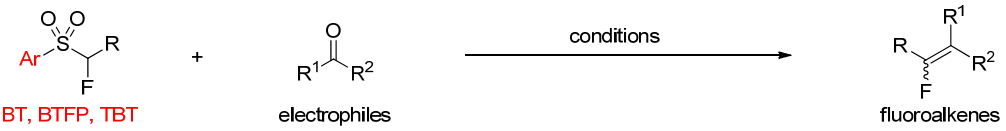


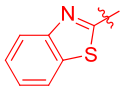
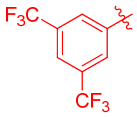
lab	R	base	carbonyl electrophile	yield (%)	*E*/*Z* ratio
Penne	CO_2Me	*n*-BuLi	R^1 = alkyl, vinyl, aryl and R^2 = H	55–95	49:1
Takeuchi	SO_2Ph	NaH	R^1 = alkyl, vinyl, aryl and R^2 = H PhCOMe, MeCOMe, cyclohexanone, *β*-ionone	64–95	1:1 to 100:0
Desmarteau	CN	*n*-BuLi	R^1 = alkyl, vinyl, aryl and R^2 = H R^1 = alkyl, vinyl, aryl and R^2 = Me	30–58	2:1 to 3:7
Tsai	Ph	LDA	R^1 = alkyl, aryl and R^2 = H PhCOMe, EtCOMe, cyclohexanone	50–76	1.5:1 to 1:4
Hammond		LDA	R^1 = alkyl, vinyl, aryl, alkynyl and R^2 = H PhCOMe, cyclohexanone	74–90	2.4:1 to 1:2

Julia-Kocienski olefinations represent common approaches for the formation of fluoroalkene derivatives. The use of electron-withdrawing aryl sulfones increases the reactivity of reagents toward carbonyl compounds and allows the reaction to proceed under mild conditions. Various fluorinated aryl sulfone reagents have been explored for realizing the transformation. The Zajc group prepared a series of α-EWG-embedded α-fluorobenzothiazolyl (BT)-derived sulfones and condensed these reagents with aldehydes to generate fluoroalkenes as a mixture of *E*/*Z* isomers (Scheme 2.7A).[17a] In 2015, the same group reported a stereoselective synthesis of 4-(1-fluorovinyl)triazoles using a second-generation Julia-Kocienski reagent, α-triazole-BT sulfone, which provided the *E*-isomer with DBU as a base and the *Z*-isomer with LHMDS as a base.[17b] Additionally, the Nájera[17c] and Hu[17d] labs independently developed 3,5-bis(trifluoromethyl)phenyl (BTFP)- and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT)-sulfones for accessing functionalized fluoroalkenes with low to modest stereoselectivity. To improve *E*/*Z* selectivity, the Lequeux[17e] and Hu[17f] groups applied a pyrimidinylsulfone-directed condensation with aldehydes and a synergistic cooperation of fluorosulfoximines and nitrones for realizing stereoselective synthesis of *Z*-fluoroalkenes (>98%), respectively (Scheme 2.7B).

Scheme 2.7. Julia-Kocienski Olefination Reactions to Access Functionalized Fluoroalkenes

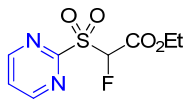
A) Modified Julia-Kocienski Olefinations of Various Substituted Aryl Sulfones



Lab	Ar	R	carbonyl electrophiles	condition	yield (%)	*E*/*Z* ratio
Zajc		Ph, CO_2t-Bu, SO_2Ph, CN, CON(OMe)Me	R^1 = (hetero)aryl, vinyl, alkyl R^2 = H (in most cases)	DBU or NaH, THF or DCM, rt or LHMDS, THF, 0 °C	59–99	2:1 to 1:99
Nájera		Me, *t*-Bu	R^1 = aryl, alkyl R^2 = H	TBAB (cat.) K_2CO_3, DMF, rt	42–99	4:1 to 1:99
Hu		H, Et, *n*-Hex, *i*-Bu, allyl, SO_2Ph, CO_2Et	R^1 = aryl, alkyl, R^2 = H R^1, R^2 = aryl, alkyl	LiHMDS, HMPA, THF, 0 °C or DBU, THF or DCM (R = EWG)	48–90	2:1 to 1:3

B) Highly Stereoselective Julia-Kocienski Olefinations

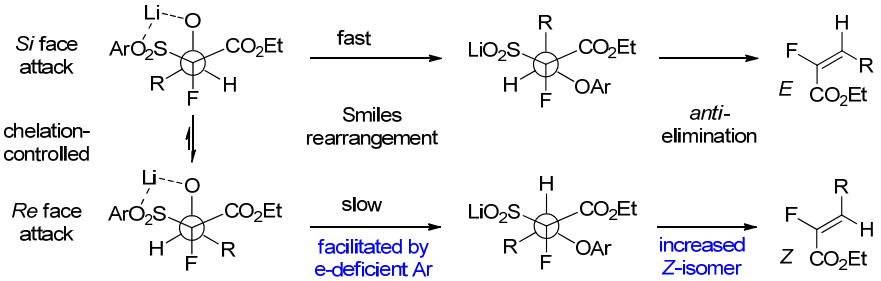
Lequeux (2014):



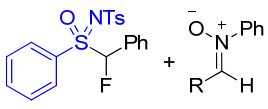
Pym

52–87%

E/*Z* < 1:43



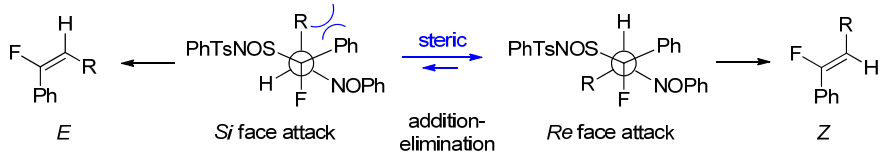
Hu (2009):



sulfoximines nitrones

29–94%

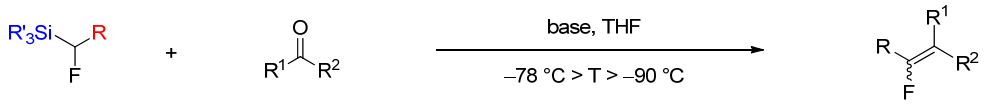
E/*Z* < 1:45



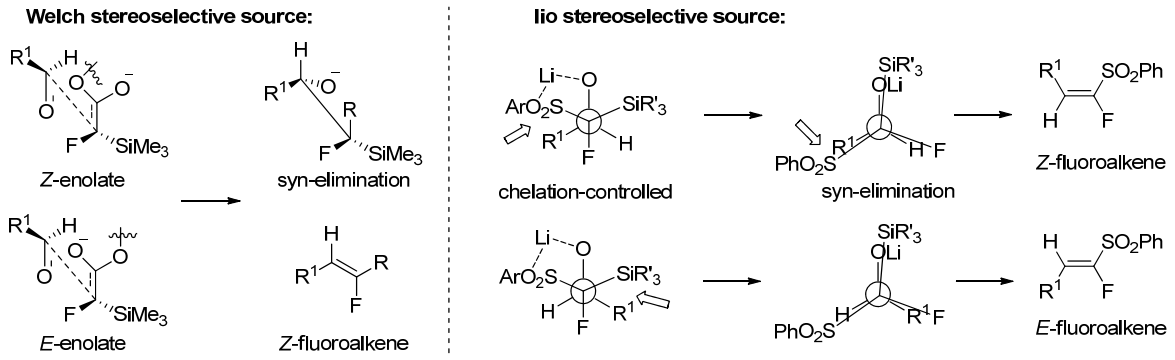
Peterson olefination reactions generally provide comparable yields and stereoselectivity compared to HWE and Julia reactions, and therefore they are less discussed in literature. The Welch lab employed a bulky α-fluoro-α-(trimethylsilyl)acetate in coupling reactions of carbonyl groups to access *Z*-selective fluoroalkenes through a open transition state irregardless of the enolate geometry (Scheme 2.8).[18a,b] The Iio group reported the reactions of α-fluoro-α-silyl sulfones with aldehydes to generate *E*-selective fluoroalkenes *via* a chelated four-centered transition state.[18c] In 2008, Mukaiyama disclosed a Lewis base-

catalyzed fluoroolefination of fluoro(trimethylsilyl)ketene trimethylsilyl acetal for constructing *Z*-fluoroalkenes (>98%).[18d]

Scheme 2.8. Stereoselective Peterson Olefinaations to Access Fluoroalkenes



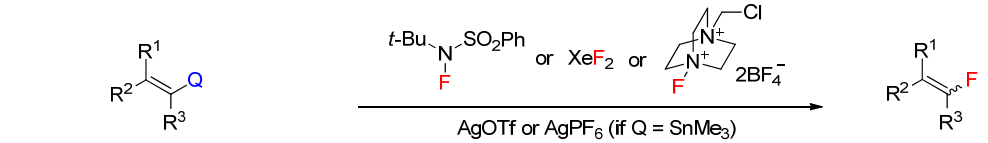
Lab	R'	R	R^1, R^2	base	yield (%)	*E*/*Z* ratio
Welch	Me	CO_2mesityl, CO_2*t*-Bu	aryl, vinyl, alkyl, H	LDA, NaHMDS, KO*t*-Bu	28–90	1:1 to *Z* only
Iio	*t*-Bu	SO_2Ph	aryl, alkyl, H	*n*-BuLi	34–65	3:1 to 20:1



2.2.5 Electrophilic Fluorination of Alkenylmetal Species

This type of reactions utilizes alkenylmetal species, including alkenyllithiums,[19a] alkenylstannanes,[19b] alkenylsilanes,[19c] and alkenylboronic acid derivatives,[19d] to couple with electrophilic fluorinating reagents XeF_2, Selectfluor®, and *N*-fluoro-sulfonamides for accessing fluorinated alkenes (Scheme 2.9). However, these methods typically encounter two problems: 1) the formation of protonated alkenes and 2) low *E*/*Z* selectivity, which increases the difficulty of compound purification.

Scheme 2.9. Electrophilic Fluorination to Access Fluorinated Alkenes

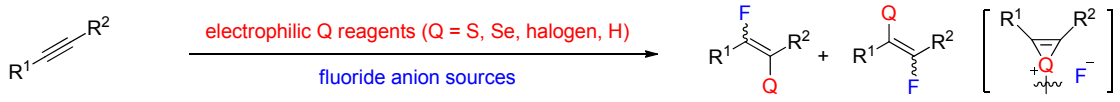


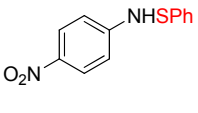
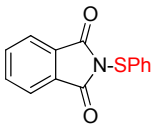
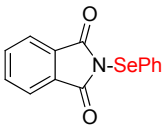
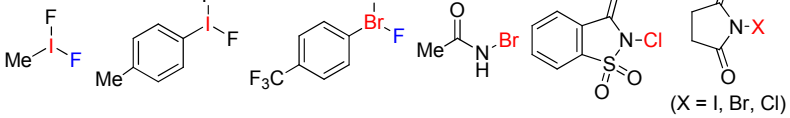
Q = halogen (metal-halo exchange)
Li, $SnMe_3$, $SiMe_3$, BF_3K
R^1, R^2, R^3 = H, alkyl, aryl

2.2.6 Monofluorofunctionalization of Alkynes

Monofluorofunctionalization of alkynes concurrently incorporates a fluorine atom and a functional group into the molecules, and represents an important and efficient strategy for accessing highly functionalized fluorinated alkenes, which enable further elaboration to produce complex fluorine-containing molecules. Many research groups have explored this area and developed a variety of methods including, fluorosulfenylation,[20a] fluoroselenation,[20a] halofluorination,[20a] hydrofluorination,[20b–d] and transition metal-catalyzed processes for introducing a fluorine atom followed by forming a C–C bond,[20a] whose methods were reviewed in 2015 (Scheme 2.10).[20a] However, these transformations have some deficiencies. While aromatic unsymmetric alkynes followed Markovnikov's rule to generate one regioisomer rather than the other one, aliphatic unsymmetric alkynes provided a mixture of regioisomers in most cases. Moreover, the reactions with unactivated alkynes require the use of a strong fluoride source such as pyridinium poly(hydrogen fluoride), and the use of excess HF reagents cause the formation of *gem*-difluorides (-CF_2CH_2-) instead of fluoroalkenes (-CF=CH-).

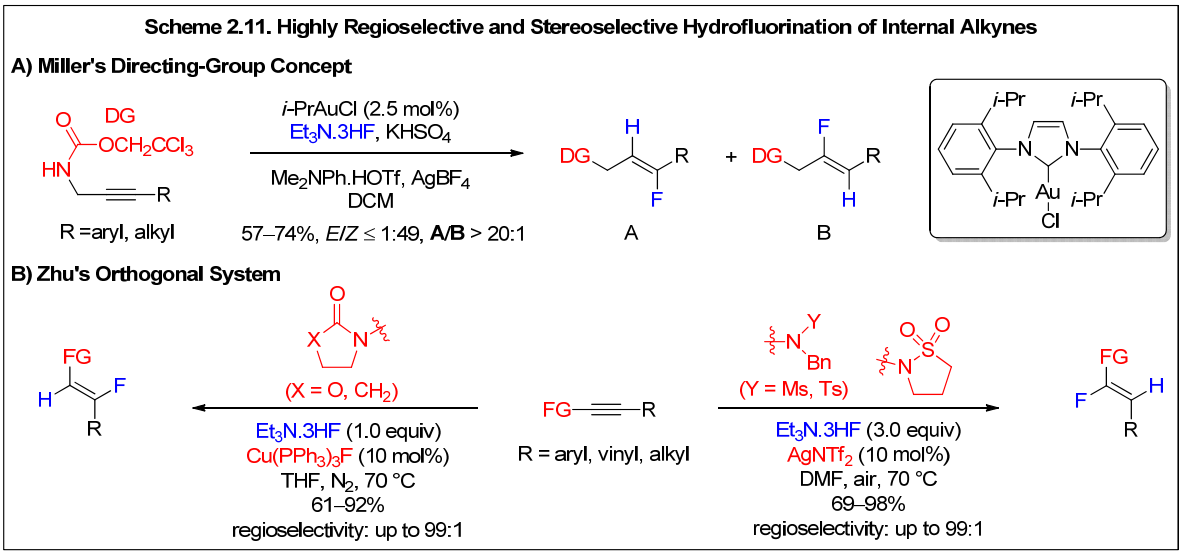
Scheme 2.10. Monofluorofunctionalization of Alkynes to Access a Variety of Fluoroalkenes



fluorosulfenylation Q = S	electrophilic sulfur reagents		
	fluoride anions	$BF_3.Et_2O$, Bu_4NBF_4	pyridine.9HF
fluoroselenation Q = Se	electrophilic selenium reagents		PhSeF (*in situ* from PhSeBr, AgF $TolIF_2$, $(PhSe)_2$ XeF_2, $(PhSe)_2$)
	fluoride anions	$Et_3N.3HF$	
halofluorination Q = I, Br, Cl	electrophilic halogen reagents		(X = I, Br, Cl)
	fluoride anions	HF (cat.) / $Et_3N.5HF$ / $BF_3.i\text{-}Pr_2O$ / HF / pyridine.HF	pyridine.HF
hydrofluorination Q = H R^2 = EWG, NRR', SR, in most cases	electrophilic hydrofluorinating reagents	CsF/H_2O / 20% aq HF or pyridine.HF / AgF/H_2O / $Et_3N.3HF$ / $Et_3N.3HF/NH_4BF_4$	DMPU.HF
	additives/catalysts	AgF / $BF_3.Et_2O$ or TiF_4 / $[\{Au(NHC)(NEt_3)\}HF_2]$	JohnPhos-Au-phthalimide

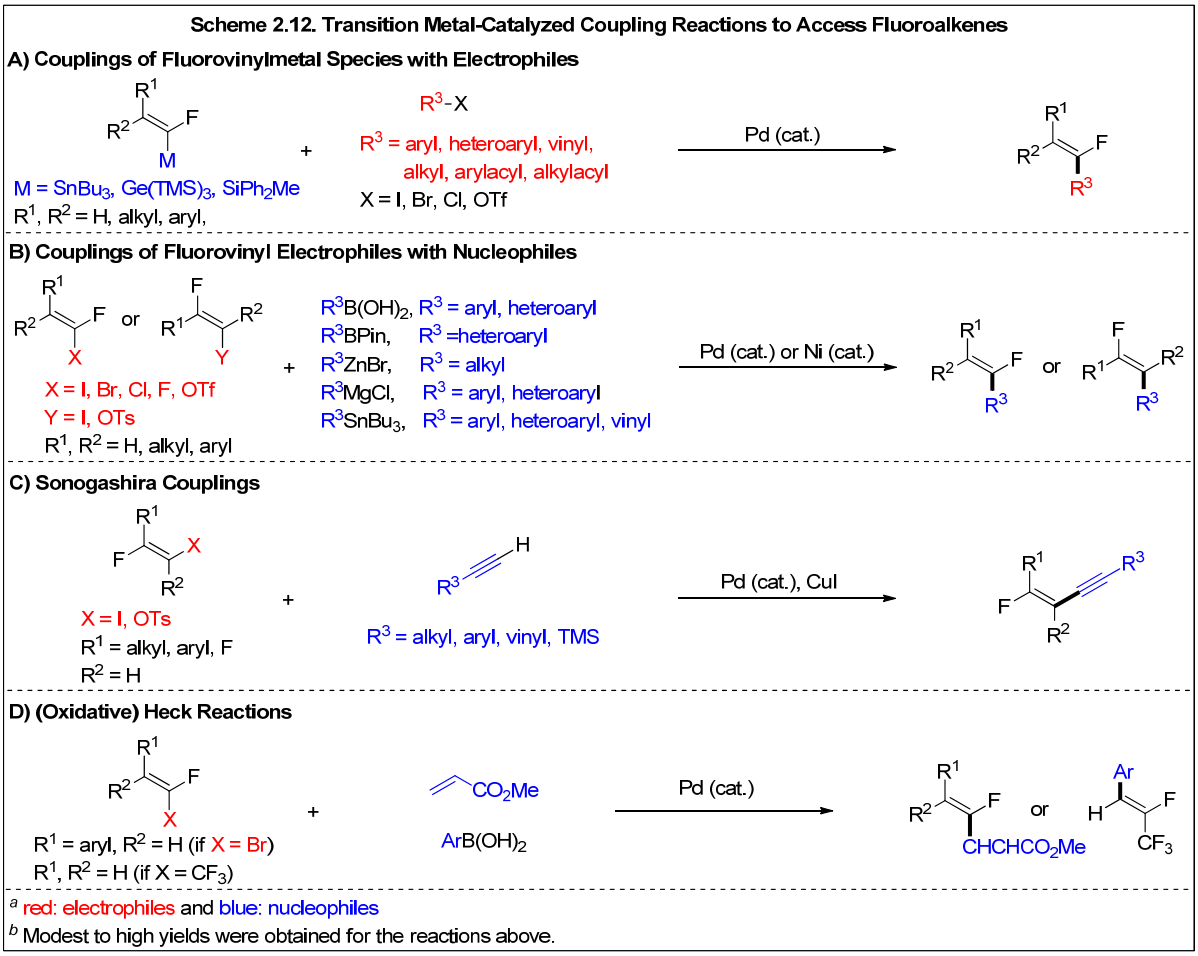
[a] The regioselectivity (Markovnikov's rule) and stereoselectivity (*E* and *Z* isomers) of products depended on the reaction conditions.

To solve these problems associated with regioselectivity, the Sadighi lab developed an electrophilic catalyst, (NHC)Au(I), to activate internal alkynes, which in turn allowed the use of less acidic $Et_3N.3HF$ reagent as a fluoride source.[21a] In 2009, the Miller group further introduced the carbamate as a directing group on the substrate to control the regioselective addition of HF to internal alkynes with high regioselectivity under the Sadighi reaction conditions (Scheme 2.11A).[21b] In 2016, the Zhu lab demonstrated an auxiliary group-mediated orthogonal catalyst system for regioselective formation of a C–F bond on α and β-position of ynamides, in which the combination of the copper(I) catalyst and an oxazolidinone group generated β-fluoroenamides, while the use of the silver(I) catalyst with a sulfonamide group afforded α-fluorinated products (Scheme 2.11B).[21c]



2.2.7 Transition Metal-Catalyzed Cross-Coupling Reactions

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



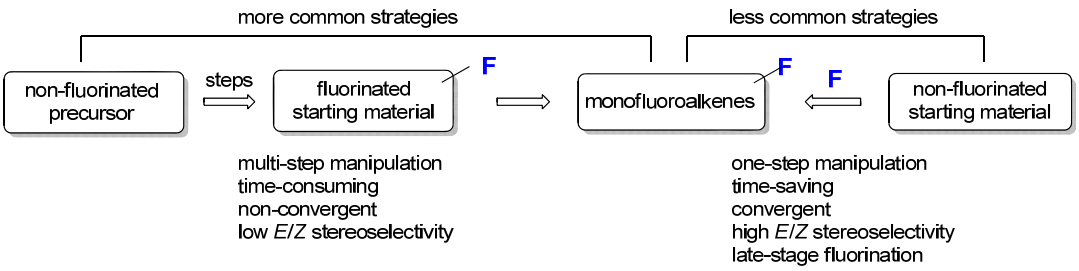
2.2.8 Miscellaneous Methods

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

2.3 Shapiro Fluorination to Access Fluoroalkenes

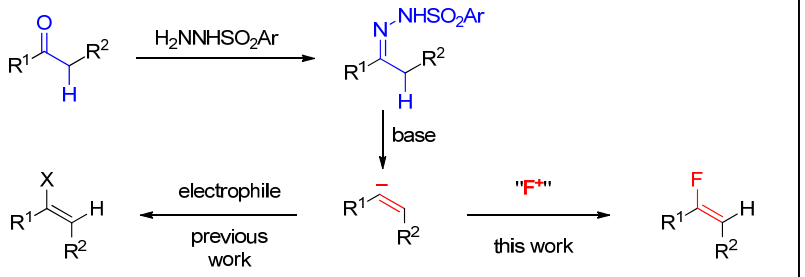
Despite the many methods that have been developed to access fluoroalkenes, convergent and straightforward strategies are desirable, especially for introducing the fluoroalkene motif at a late stage of a synthesis through modification of a compound already in hand and using commercially available fluorinating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

Scheme 2.13. Comparison of Current Methods to Access Fluoroalkenes



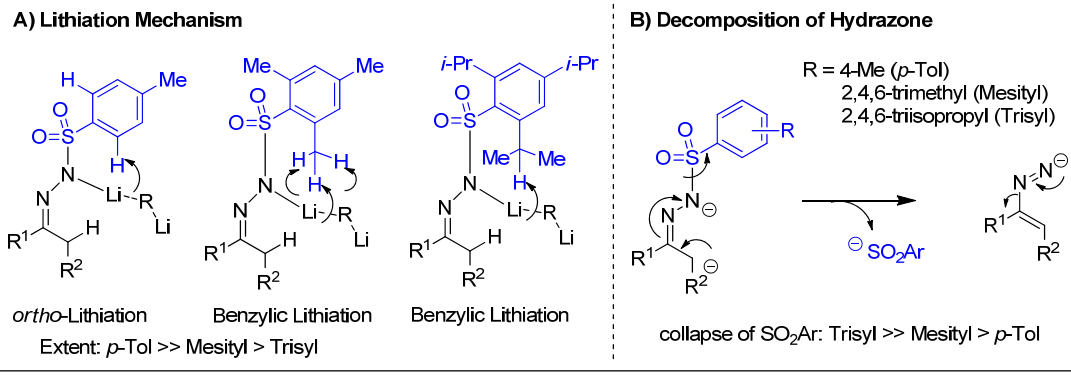
It was envisaged that fluoroolefins could be accessed through a Shapiro fluorination reaction (Scheme 2.14).[24] The Shapiro reaction has been widely applied in the synthesis of natural products,[25] and for the preparation of polysubstituted alkenes,[26] many of which are not easily accessed by other means. A prototypical Shapiro reaction involves: 1) condensation of an *N*-sulfonyl hydrazide with a ketone to provide a sulfonyl hydrazone; 2) treatment of the sulfonyl hydrazone with a base to provide a vinyl lithium intermediate; and 3) trapping of the vinyl anion with H^+ to afford an alkene-based product.[24] Alternatively, the *in situ* formed alkenyllithium intermediate can also be trapped with a variety of electrophiles to generate allylic alcohols, acrylic acids, acrylic aldehydes, vinylsilanes, and vinyl iodides and bromides.[27] However, the Shapiro reaction has not been employed to access fluoroakenes. Herein, we describe a Shapiro fluorination reaction to provide fluoroalkenes in high diastereoselectivity (Scheme 2.14).

Scheme 2.14. Shapiro Reactions Convert Ketones to Functionalized Alkenes



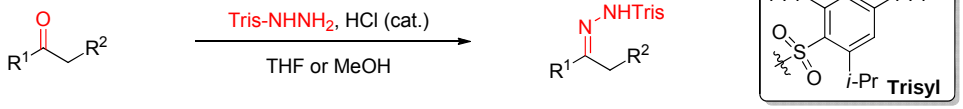
The Shapiro fluorination reaction was scouted using a variety of commercially available electrophilic fluorinating reagents,[28] and biphenyl 2,4,6-triisopropylbenzenesulfonyl (trisyl) hydrazone (**2.1a** or also called (*E*)-*N'*-(1-([1,1'-biphenyl]-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide) as a test substrate. Trisyl hydrazones were employed instead of tosylsulfonyl or mesitylsulfonyl moieties, because the former group: 1) does not undergo *ortho*-lithiation or α-lithiation, which allows for the reaction to proceed using fewer equivalents of base and electrophilic trapping agent (Scheme 2.15A); [29] and 2) decomposes more easily than unhindered aryl hydrazones, a phenomenon that likely arises from the release of steric compression at the transition state (Scheme 2.15B).[30]

Scheme 2.15. Trisyl Hydrazones Provide Beneficial Reactivity Compared to Other Hydrazones

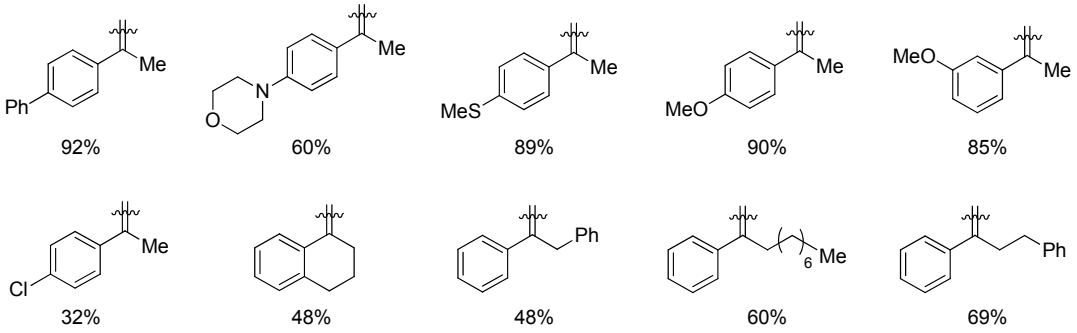


The preparation of trisyl hydrazones involved condensation reactions of ketones with 2,4,6-triisopropylbenzenesulfonyl hydrazide in the presence of catalytic amount of hydrochloric acid, and the conventional procedure provided hydrazone products in reasonable yields (Scheme 2.16).[24]

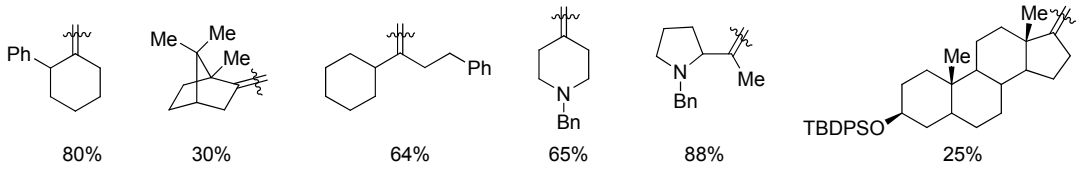
Scheme 2.16. General Procedure for Preparing Acetophenone-Derived and Aliphatic Trisyl Hydrazones



A) Acetophenone-Derived Trisyl Hydrazones

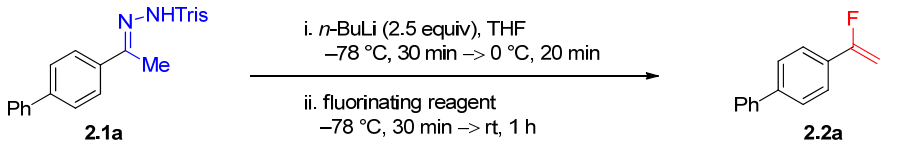


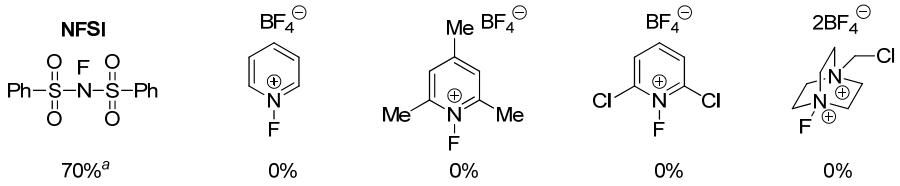
B) Aliphatic Trisyl Hydrazones



Decomposition of the trisyl hydrazone (**2.1a**) was accomplished by lithiation with 2.5 equivalents of *n*-butyllithium (*n*-BuLi) in THF from –78 to 0 °C, followed by cooling to –78 °C for the addition of the electrophilic fluorinating reagents. No fluorinated product was observed by ^{19}F NMR when the *in situ* formed vinyl anion was allowed to react with *N*-fluoropyridinium salts or selectfluor. Potentially, the poor reactivity of these reagents arose from the low solubility of the ionic reagents in THF at low temperature. In contrast, employment of *N*-fluorobenzenesulfonimide (NFSI), a neutral fluorinating agent that maintains good solubility in ethers and hydrocarbon solvents at lower temperature,[31] provided the desired fluoroalkene product in 70% yield based on ^{19}F NMR spectroscopy (Scheme 2.17).

Scheme 2.17. Screening of Different Electrophilic Fluorinating Reagents



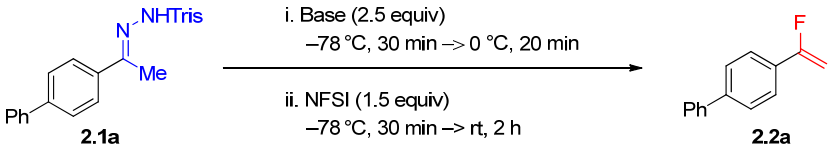


Features of NFSI:
> better solubility in nonpolar solvents and low temperatures
> soft and neutral fluorinating reagents

[a] Yields were determined by ^{19}F NMR analysis with α,α,α-trifluorotoluene as an internal standard.

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

Table 2.2. Optimization of the Shapiro Fluorination Reaction[a]



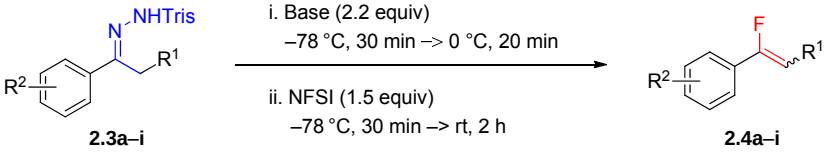
2.1a **2.2a**

entry	base	solvent	NFSI dissolved in	yield (%)[b]
1	*n*-BuLi	THF	THF	70
2	*n*-BuLi	THF	toluene	67
3	*n*-BuLi	THF	solid added	54
4	*n*-BuLi	THF/TMEDA (4:1)	THF	68
5[c]	*n*-BuLi	TMEDA	toluene	48
6	*n*-BuLi	Hexane/TMEDA (9:1)	toluene	53
7[c]	*n*-BuLi	DME	toluene	50
8	*s*-BuLi	THF	THF	68
9	CH_3Li	THF	THF	28
10[d]	*n*-BuLi	THF	THF	18
11[e]	*n*-BuLi	THF	THF	68
12[f]	*n*-BuLi	THF	THF	65
13[g]	*n*-BuLi	THF	THF	78 (75)[h]

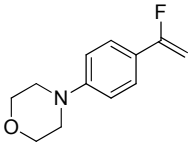
[a] Standard reaction conditions: **2.1a** (1.0 equiv, 0.20 M solution), base (2.5 equiv), NFSI (1.5 equiv, 0.50 M THF solution or 0.20 M toluene solution). [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c] Reaction temperatures of –60 °C for 30 min followed by 0 °C for 20 min. [d] HMPA (1.0 equiv) was added during lithiation. [e] NFSI (2.0 equiv). [f] 0.10 M solution was used in the step i. [g] *n*-BuLi (2.2 equiv). [h] Isolated yield of material deemed to be >95% pure by ^1H NMR.

Using the optimized reaction sequence, several acetophenone-derived substrates afforded fluoroalkene products (Scheme 2.18). Electron-rich aryl-substituted trisyl hydrazones including *para*-morpholine, –SMe and –OMe were converted to fluoroalkenes **2.4a**–**d**. The *para*-chloro-substituted fluorostyrene (**2.4e**) was provided in 52% yield. Reactions of substrates bearing substituents at the *β*-position provided *Z*-fluoroalkene products in good to excellent diastereoselectivitites (**2.4g**–**i**). Presumably, the stereochemistry of these reactions was dictated by the unfavorable steric repulsion of the *syn* arrangement of the organic substituents. In contrast, the *E*-fluoroalkene was accessed for a cyclic ketone (**2.4f**). However, no fluoroalkene products were obtained in reactions of substrates bearing *para*- and *meta*-CF_3 and *meta*-chloro electron-withdrawing groups. As control experiments, subjection of these three substrates to the Shapiro conditions and quenching of the presumed vinyllithium intermediate with D_2O did not provide the anticipated deuterated or protonated alkenes (GC-MS), indicating that these three substrates were not compatible with the lithiation step.[32]

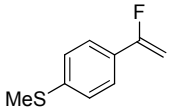
Scheme 2.18. Shapiro Fluorination of Acetophenone-Derived Trisyl Hydrazones to Provide Fluorostyrenes[a]



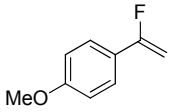
2.3a–i **2.4a–i**



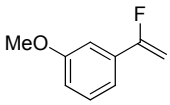
2.4a[b], 75% (67%)



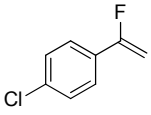
2.4b, 68% (65%)



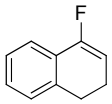
2.4c, 67% (54%)



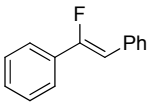
2.4d[c], 67% (43%)



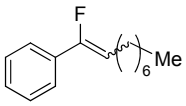
2.4e, 52% (42%)



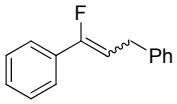
2.4f, 57% (50%)



2.4g[d], 87% (79%)
(*Z* only)[e]



2.4h, 81% (77%)
(*E*:*Z* = 1:8.5)[e]

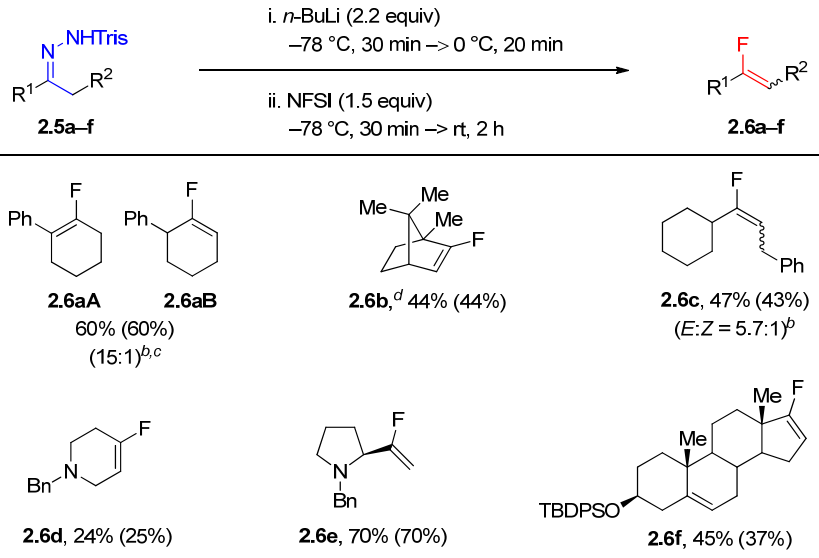


2.4i, 45% (43%)
(*E*:*Z* = 1:6.5)[e]

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

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

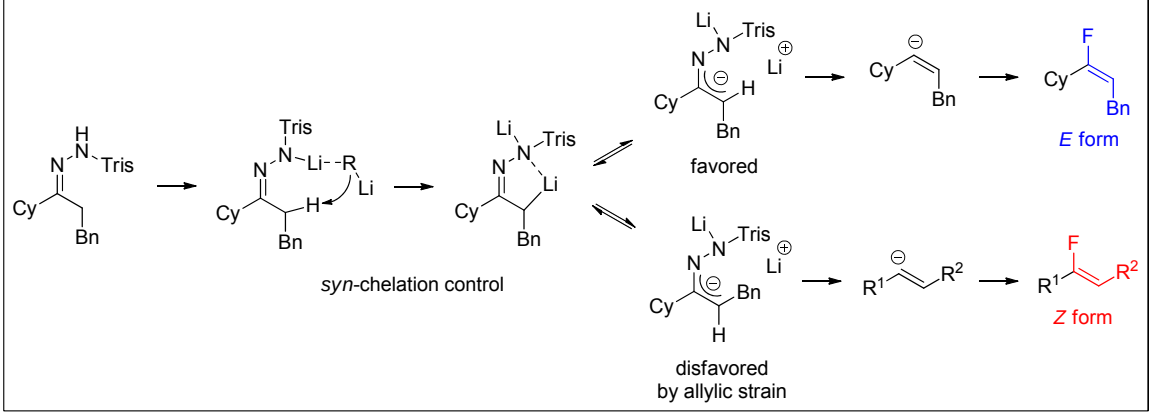
Scheme 2.19. Shapiro Fluorination of Aliphatic Trisyl Hydrazones to Provide Fluoroalkenes[a]



[a] Standard reaction conditions: **2.5a–f** (1.0 equiv, 0.20 M solution in THF), *n*-BuLi (2.2 equiv), NFSI (1.5 equiv, 0.50 M solution in THF). Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard (average of two runs), and the figure in the parenthesis represents the isolated yield (average of two runs). [b] The ratios of isomers were determined by integration of the ^{19}F NMR spectrum of the crude reaction mixture. [c] *t*-BuLi (2.2 equiv) afforded improved regioselectivity. [d] *s*-BuLi (2.2 equiv) was used.

The substrate **2.5c** afforded *E*-fluoroalkene in 5.7:1 diastereoselectivity. In contrast to the *Z*-selectivity observed for products **2.4g–i**, the reaction to selectively generate *E*-**2.6c** seems to be controlled by a *syn*-dianion chelation effect, which is frequently observed in Shapiro reactions (Scheme 2.20).[24] The chelation of lithium bases to nitrogen of the hydrazone enables *syn*-deprotonation, which puts the alkyl group away from the hydrazone to reduce allylic strain. Subsequently, the release of nitrogen gas from the dianion forms the configurationally stable *Z*-vinyl anion that generates the *E*-fluoroalkene upon trapping with electrophilic F sources (Scheme 2.20).[24,27b]

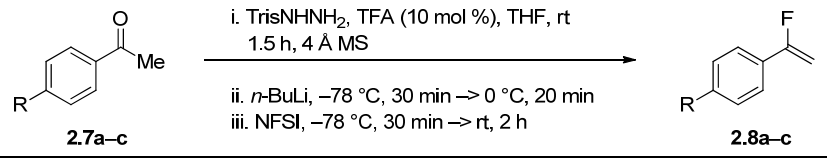
Scheme 2.20. *syn*-Dianion Chelation Effect Favored the Formation of *E*-Fluoroalkenes



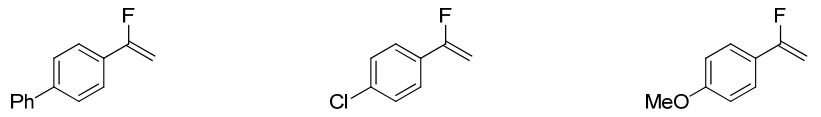
Additionally, amines protected with benzyl groups were compatible with the reaction conditions, and afforded 28%–70% yields, depending on the substrates (**2.6d**–**e** in Scheme 2.19).[33] Pyrrolidine-based derivative **2.6e** could prove useful for strategic replacement of proline-based residues to form fluorinated peptide-based probes with distinct biophysical properties. Finally, the method was used to rapidly access new fluorinated analogues of natural products, including camphor and a protected steroid (**2.6b** and **2.6f**). However, the silyl protecting group was not necessary, and the steroid substrate bearing an unprotected hydroxyl group provided 33% yield by ^{19}F NMR analysis (not shown in Scheme 2.19, 3.2 equiv *n*-BuLi employed). Thus, the present reaction provides a new entrypoint for the preparation of fluorinated steroids, which are clinically employed for the treatment of various disease states.[34]

In order to accomplish the direct conversion of ketones to fluoroalkenes, a one-pot reaction sequence was developed (Scheme 2.21). The use of an acid catalyst, in combination with molecular sieves, facilitated the initial condensation reaction, and was compatible with the subsequent lithiation and fluorination steps. Using this one-pot procedure, yields of the fluoroalkene products were comparable with those from the isolated hydrazones (**2.8a** vs. **2.2a**; **2.8b** vs. **2.4e**; **2.8c** vs. **2.4c**). This sequence enables easy access to a variety of fluoroalkenes from ketones without purification of intermediates, and it is anticipated that this one-pot procedure could be optimized to access nonstyrenyl fluoroalkenes by improving the efficiency of condensation reactions of ketones with trisyl hydrazides.

Scheme 2.21. One-Pot Sequence Converting Ketones to Fluoroalkenes[a,b]



2.7a–c **2.8a–c**



2.8a, 70% **2.8b**, 46% **2.8c**, 54%

[a] Standard reaction conditions: i. **2.7a–c** (1.0 equiv, 0.50 M solution in THF), $TrisNHNH_2$ (1.0 equiv), TFA (0.1 equiv), rt, 1.5 h; ii. THF (1.5 mL) for dilution, 4Å molecular sieve (800 mg/mmol), *n*-BuLi (3.0 equiv), –78 °C, 30 min –> 0 °C, 20 min; iii. NFSI (1.5 equiv, 0.50 M solution in THF), –78 °C, 30 min –> rt, 2 h. [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

2.4 Conclusion

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

2.5 References for Chapter 2

[1] (a) Sciotti, R. J.; Pliushchev, M.; Wiedeman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. "The Synthesis and Biological Evaluation of A Novel Series of Antimicrobials of the Oxazolidinone Class" *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2121–2123. (b) Asahina, Y.; Iwase, K.; Iinuma, F.; Hosaka, M.; Ishizaki, T. "Synthesis and Antibacterial Activity of 1-(2-Fluorovinyl)-7-Substituted-4-Quinolone-3-Carboxylic Acid Derivatives, Conformationally Restricted Analogues of Fleroxacin" *J. Med. Chem*. **2005**, *48*, 3194–3202. (c) Osada, S.; Sano, S.; Ueyama, M.; Chuman, Y.; Kodama, H.; Sakaguchi, K. "Fluoroalkene Modification of Mercaptoacetamide-Based Histone Deacetylase Inhibitors" *Bioorg. Med. Chem*. **2010**, *18*, 605–611. (d) Kanazawa, J.; Takahashi, T.; Akinaga, S.; Tamaoki, T.; Okabe, M. "The Relationship between the Antitumor Activity and the Ribonucleotide Reductase Inhibitory Activity of (*E*)-2'-Deoxy-2'-(fluoromethylene) Cytidine, MDL 101, 731" *Anti-Cancer Drugs*, **1998**, *9*, 653–657. (e) Edmondson, S. D.; Wei, L.; Xu, J.; Shang, J.; Xu, S.; Pang, J.; Chaudhary, A.; Dean, D. C.; He, H.; Leiting, B.; Lyons, K. A.; Patel, R. A.; Patel, S. B.; Scapin, G.; Wu, J. K.; Beconi, M. G.; Thornberry, N. A.; Weber, A. E. "Fluoroolefins as Amide Bond Mimics in Dipeptidyl Peptidase IV Inhibitors" *Bioorg. Med. Chem. Lett*. **2008**, *18*, 2409–2413. (f) Deng, T.; Shan, S.; Li, Z.-B.; Wu, Z.-W.; Liao, C.-Z.; Ko, B.; Lu, X.-P.; Cheng, J.; Ning, Z.-Q. "A New Retinoid-like Compound That Activates Peroxisome Proliferator-Activated Receptors and Lowers Blood Glucose in Diabetic Mice" *Biol. Pharm. Bull*. **2005**, *28*, 1192–1196. (g) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. "Peptide Bond Mimicry by (*E*)-Alkene and (*Z*)-Fluoroalkene Peptide Isosteres: Synthesis and Bioevaluation of α-Helical Anti-HIV Peptide Analogues" *Org. Biomol. Chem*. **2009**, *7*, 2872–2877.

[2] (a) 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 Analogs" *Tetrahedron* **1986**, *42*, 2101–2110. (b) Cieplack, P.; Kollmann, P. A.; Radomski, J. P. "Molecular Design of Fluorine-Containing Peptide Mimetics" *ACS Symposium Series* **1996**, *639*, 143–156. (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*, 6088–6089. (d) Taguchi, T.; Yanai, H. *Fluorinated Moieties for Replacement of Amide and Peptide Bonds*, in: *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, UK, **2009**, pp. 257–290.

[3] (a) O'Hagan, D.; Rzepa, H. S. "Some Influences of Fluorine in Bioorganic Chemistry" *Chem. Commun*. **1997**, 645–652. (b) Bégué. J.-P., Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: Hoboken, NJ, **2008**.

[4] 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*, 11120–11129.

[5] (a) Gante, J. "Peptidomimetics-Tailored Enzyme Inhibitors" *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 1699–1720. (b) 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*, 14020–14024. (c) Van der Veken, P.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpe, S.; Haemers, A.; Augustyns, K. "Fluoro-Olefins as Peptidomimetic Inhibitors of Dipeptidyl Peptidases" *J. Med. Chem*. **2005**, *48*, 1768–1780.

[6] Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K. I.; 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*, 613–616.

[7] (a) Yanai, H.; Taguchi, T. "Synthetic Methods for Fluorinated Olefins" *Eur. J. Org. Chem*. **2011**, 5939–5954. (b) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. "Synthetic Approaches to Monofluoroalkenes" *Chem. Soc. Rev*. **2011**, *40*, 2867–2908.

[8] (a) Ernet, T.; Maulitz, A. H.; Wurthwein, E.-U.; Haufe, G. "Dienophilic Reactivity of Perfluoroalkenyl Ketones in Diels-Alder Reactions" *J. Chem. Soc., Perkin Trans. 1* **2001**, 1929–1938. (b) Haufe, G. "Vinyl Fluorides in Cycloadditions" *ACS Symposium Series* **2005**, *911*, 155–172. (c) Lam, Y.-H.; Stanway, S. J.; Gouverneur, V. "Recent Progress in the Use of Fluoroorganic Compounds in Pericyclic Reactions" *Tetrahedron* **2009**, *65*, 9905–9933.

[9] (a) Haufe, G.; Rosen, T. C.; Meyer, O. G. J.; Frohlich, R.; Rissanen, K. "Synthesis, Reactions and Structural Features of Monofluorinated Cyclopropanecarboxylates" *J. Fluorine Chem*. **2002**, *114*, 189–198. (b) Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Haufe, G. "Fluorinated Phenylcyclopropylamines as Inhibitors of Monoamine Oxidases" *ChemBiochem* **2004**, *5*, 1033–1043. (c) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. "Syntheses and Applications of Monofluorinated Cyclopropanes" *Chem. Eur. J*. **2012**, *18*, 14904–14917. (d) Hirotaki, K.; Takehiro, Y.; Kamaishi, R.; Yamada, Y.; Hanamoto, T. "Synthesis of Mono-Fluorinated Functionalized Cyclopropanes and Aziridines Using the α-Fluorovinyl Diphenyl Sulfonium Salt" *Chem. Commun*. **2013**, *49*, 7965–7967. (e) Pons, A.; Beucher, H.; Ivashkin, P.; Lemonnier, G.; Poisson, T.; Charette, A. B.; Jubault, P.; Pannecoucke, X. "Rhodium-Catalyzed Cyclopropanation of Fluorinated Olefins: A Straightforward Route to Highly Functionalized Fluorocyclopropanes" *Org. Lett*. **2015**, *17*, 1790–1793.

[10] (a) Souzy, R.; Ameduri, B.; Boutevin, B. "Synthesis and (Co)polymerization of Monofluoro, Difluoro, Trifluorostyrene and ((Trifluorovinyl)oxy)benzene" *Prog. Polym. Sci*. **2004**, *29*, 75–106. (b) Babudri, F.; Cardone, A.; Farinola, G. M.; Martinelli, C.; Mendichi, R.; Naso, F.; Striccoli, M. "Synthesis of Poly(arylenevinylene)s with Fluorinated Vinylene Units" *Eur. J. Org. Chem*. **2008**, 1977–1982. (c) Walkowiak-Kulikowska, J.; Boschet, F.; Kostov, G.; Gouverneur, V.; Ameduri, B. "On the Reactivity of α-Trifluoromethylstyrene in Radical Copolymerizations with Various Fluoroalkenes" *European Polymer Journal* **2016**, *84*, 612–621.

[11] (a) McCarthy, J. R.; Matthews, D. P.; Barney, C. L. "A New Synthesis of 2-Fluoro-1-olefins" *Tetrahedron Lett*. **1990**, *31*, 973–976. (b) Usuki, Y.; Iwaoka, M.; Tomoda, S. "A New Synthesis of α-Fluoro-α,β-unsaturated Ketones and Esters Based on Organoselenium Methodology" *J. Chem. Soc., Chem. Commun*. **1992**, 1148–1150. (c) Nguyen, T.; Leroy, J.; Wakselman, C. "An Expeditious Synthesis of 3-Fluoroacrylic Acid" *J. Org. Chem*. **1993**, *58*, 3772–3774. (d) Hedhli, A.; Baklouti, A. "Action of Potassium Fluoride and DBU on β-Fluoro-γ,δ-unsaturated *p*-Toluenesulfonates: A Convenient Route to Conjugated 2-Fluoroalkadienes" *Tetrahedron Lett*. **1995**, *36*, 4433–4436. (e) Sasson, R.; Rozen, S. "Bromofluorination of Olefins Using BrF_3; An Efficient Route for Fluoroalkenes and Fluoroamines" *J. Fluorine Chem*. **2006**, *127*, 962–965. (f) Wong, O. A.; Shi, Y. "Asymmetric Epoxidation of Fluoroolefins by Chiral Dioxirane. Fluorine Effect on Enantioselectivity" *J. Org. Chem*. **2009**, *74*, 8377–8380. (g) Reutrakul, V.; Rukachaisirikul, V. "Fluoromethyl Phenyl Sulfoxide: Highly Convenient Synthesis of Vinyl Fluorides and Fluoromethyl Ketones" *Tetrahedron Lett*. **1983**, *24*, 725–728. (h) Uno, H.; Semba, F.; Tasaka, T.; Suzuki, H. "A Novel Generation and Behavior of Alkylfluorocarbenoids from α,α-Chlorofluoroalkyl Sulfoxides" *Chem. Lett*. **1989**, 309–312. (i) Krishnan, G.; Sampson, P. *Tetrahedron Lett*. **1990**, *31*, 5609–5612. (j) Allmendinger, T. "Ethyl Phenylsulfinylfluoroacetate, A New and Versatile Reagent for the Preparation of α-Fluoro-α,β-unsaturated Carboxylic Acid Esters" *Tetrahedron* **1991**, *47*, 4905–4914. (k) Prakash, G. K. S.; 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*, 1127–1130. (l) Sano, K.; Fukuhara, T.; Hara, S. *J. Fluorine Chem*. **2009**, *130*, 708–713.

[12] (a) Kirihara, M.; Takuwa, T.; Okumura, M.; Wakikawa, T.; Takahata, H.; Momose, T.; Takeuchi, Y.; Nemoto, H. "α-Bromo-α,α-difluoroallyl Derivatives as Synthetic Intermediates: Nucleophilic Substitution of α-Bromo-α,α-difluoroallyl Derivatives in the Presence of Palladium Catalysts" *Chem. Pharm. Bull*. **2000**, *48*, 885–888. (b) 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*, 3465–3468. (c) Pigeon, X.; Bergeron, M.; Barabé, F.;

Dubé, P.; Frost, H. N.; Paquin, J.-F. "Activation of Allylic C–F Bonds: Palladium-Catalyzed Allylic Amination of 3,3-Difluoropropenes" *Angew. Chem. Int. Ed*. **2010**, *49*, 1123–1127. (d) Zhang, H.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. "Rh-Catalyzed Allylic C–F Bond Activation: the Stereoselective Synthesis of Trisubstituted Monofluoroalkenes And a Mechanism Study" *Org. Biomol. Chem*. **2014**, *12*, 581–588. (e) Miura, T.; Ito, Y.; Murakami, M. "Synthesis of *Gem*-Difluoroalkenes *via β*-Fluoride Elimination of Organorhodium(I)" *Chem. Lett*. **2008**, *37*, 1006–1007. (f) Lin, X.; Zheng, F.; Qing, F.-L. "Regio- and Diastereoselective Nickel-Catalyzed Allylation of Aromatic Aldehydes with α-Halo-β,β-difluoropropene Derivatives" *J. Org. Chem*. **2012**, *77*, 8696–8704.

[13] (a) Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, N. "New Access to α-Substituted (*Z*)-Fluoroalkene Dipeptide Isosteres Utilizing Organocopper Reagents under 'Reduction-Oxidative Alkylation (R-OA)' Conditions" *Tetrahedron Lett*. **2001**, *42*, 5443–5446. (b) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. "SmI_2-Mediated Reduction of γ,γ-Difluoro-α,β-enoates with Application to the Synthesis of Functionalized (*Z*)-Fluoroalkene-Type Dipeptide Isosteres" *J. Org. Chem*. **2004**, *69*, 1634–1645. (c) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Honkawa, H.; Taguchi, T. "Synthesis of α-Alkylated (*Z*)-γ -Fluoro-β,γ-enoates through Organocopper Mediated Reaction of γ,γ-Difluoro-α,β-enoates: A Different Reactivity of R_3Al-Cu(I) and Me_2CuLi" *Chem. Lett*. **2002**, 28–29. (d) Yamaki, Y.; Shigenaga, A.; Tomita, K.; Narumi, T.; Fujii, N.; Otaka, A. "Synthesis of Fluoroalkene Dipeptide Isosteres by An Intramolecular Redox Reaction Utilizing *N*-Heteorocyclic Carbenes (NHCs)" *J. Org. Chem*. **2009**, *74*, 3272–3277. (e) Yamaki, Y.; Shigenaga, A.; Li, J.; Shimohigashi, Y.; Otaka, A. "Synthesis of Amide-Type Fluoroalkene Dipeptide Isosteres by An Intramolecular Redox Reaction" *J. Org. Chem*. **2009**, *74*, 3278–3285. (f) Drouin, M.; Hamel, J.-D.; Paquin, J.-F. "Exploiting 3,3-Difluoropropenes for the Synthesis of Monofluoroalkenes" *Synlett* **2016**, *27*, 821–830.

[14] (a) Hayashi, S.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. "Convenient Procedures for Conversion of Carbonyl Compounds to *Gem*-Difluoroolefins and Their Selective Reductions to Monofluoroolefins" *Chem. Lett*. **1979**, 983–986. (b) Landelle, G.; Turcotte-Savard, M.-O.; Angers, L.; Paquin, J.-F. "Stereoselective Synthesis of Both Stereoisomers of β-Fluorostyrene Derivatives from a Common Intermediate" *Org. Lett*, **2011**, *13*, 1568–1571. (c) Wu, J.; Xiao, J.; Dai, W.; Cao, S. "Synthesis of Monofluoroalkenes through Selective Hydrodefluorination of *gem*-Difluoroalkenes with Red-Al" *RSC Adv*. **2015**, *5*, 34498–34501. (d) 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*, 681–684. (e) 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. (f) 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*, 4284–4287. (g) 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" *Chem. Eur. J*. **2016**, *22*, 9902–9908. (h) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. "The Nucleophilic 5-Endo-trig Cyclization of 1,1-Difluoro-1-alkenes: Ring-Fluorinated Hetero- and Carbocycle Synthesis and Remarkable Effect of the Vinylic Fluorines on the Disfavored Process" *Synthesis*, **2002**, 1917–1936.

[15] 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*, 2811–2812.

[16] (a) Moghadam, G. E.; Penne, J. S. "Stereoselective Synthesis of *E*- α-Fluoro-α,β-unsaturated Esters by Wittig-Horner Reaction from Methyl α-(*O*,*O*-Diethylphosphono)-α-fluoroacetate. Comparison with Methyl α-(diphenylphosphinyl)-α-fluoroacetate" *Bull. Soc. Chim. Fr*. **1985**, 448–454. (b) Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y. "Diethyl 1-Fluoro-1-phenylsulfonylmethanephosphonate, a Versatile Agent for the Preparation of Monofluorinated Building Blocks" *Chem. Pharm. Bull*. **1987**, *35*, 3959–3962.

(c) Xu, Z.-Q.; Desmarteau, D. D. "A Convenient One-Pot Synthesis of α-Fluoro-α,β-unsaturated Nitriles from Diethyl Cyanofluoromethanephosphonate" *J. Chem. Soc., Perkin Trans. 1*. **1992**, 313–315. (d) Tsai, H.-J. "Synthesis of Phenyl-Substituted Fluoro-Olefins" *Tetrahedron Lett*. **1996**, *37*, 629–632. (e) Zapata, A. J.; Gu, Y. H.; Hammond, G. B. "The First α-Fluoroallenylphosphonate, the Synthesis of Conjugated Fluoroenynes, and the Stereoselective Synthesis of Vinylfluorophosphonates Using a New Multifunctional Fluorine-Containing Building Block" *J. Org. Chem*. **2000**, *65*, 227–234.

[17] (a) Zajc, B.; Kumar, R. "Synthesis of Fluoroolefins *via* Julia-Kocienski Olefination" *Synthesis* **2010**, 1822–1836. (b) Kumar, R.; Singh, G.; Todaro, L. J.; Yang, L.; Zajc, B. "*E*- or *Z*-Selective Synthesis of 4-Fluorovinyl-1,2,3-triazoles with Fluorinated Second-Generation Julia-Kocienski Reagents" *Org. Biomol. Chem*. **2015**, *13*, 1536–1549. (c) Alonso, D. A.; Fuensanta, M.; Gomez-Bengoa, E.; Nájera, C. "Highly Efficient and Stereoselective Julia-Kocienski Protocol for the Synthesis of α-Fluoro-α,β-unsaturated Esters and Weinreb Amides Employing 3,5-Bis(trifluoromethyl)phenyl (BTFP) Sulfones" *Adv. Synth. Catal*. **2008**, *350*, 1823–1829. (d) Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. "1-*tert*-Butyl-1*H*-tetrazol-5-yl Fluoromethyl Sulfone ($TBTSO_2CH_2F$): A Versatile Fluoromethylidene Synthon and Its Use in the Synthesis of Monofluorinated Alkenes *via* Julia-Kocienski Olefination" *Tetrahedron* **2010**, *66*, 5089–5100. (e) Larnaud, F.; Pfund, E.; Linclau, B.; Lequeux, T. "Stereoselective Formation of (*Z*)-2-Fluoroalkenoates *via* Julia-Kocienski Reaction of Aldehydes with Pyrimidinyl-fluoro-sulfones" *Tetrahedron*, **2014**, *70*, 5632–5639. (f) Zhang, W.; Huang, W.; Hu, J. "Highly Stereoselective Synthesis of Monofluoroalkenes from α-Fluorosulfoximines and Nitrones" *Angew. Chem. Int. Ed*. **2009**, *48*, 9858–9861.

[18] (a) Welch, J. T.; Herbert, R. W. "The Stereoselective Construction of (*Z*)-3-Aryl-2-fluoroalkenoates" *J. Org. Chem*. **1990**, *55*, 4782–4784. (b) 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*, 9613–9616. (c) Asakura, N.; Usuki, Y.; Iio, H. "A New Synthesis of α-Fluorovinylsulfones Utilizing the Peterson Olefination Methodology" *J. Fluorine Chem*. **2003**, *124*, 81–88. (d) Michida, M.; Mukaiyama, T. "A Convenient Method for the Synthesis of (*Z*)-α-Fluoroacrylates. Lewis Base-Catalyzed Carbonyl Fluoroolefination Using Fluoro(trimethylsilyl)ketene Ethyl Trimethylsilyl Acetal" *Chem. Lett*. **2008**, *37*, 890–891.

[19] (a) Lee, S. H.; Schwartz, J. "Stereospecific Synthesis of Alkenyl Fluorides (with Retention) *via* Organometallic Intermediates" *J. Am. Chem. Soc*. **1986**, *108*, 2445–2447. (b) Tius, M. A.; Kawakami, J. K. "The Reaction of XeF_2 with Trialkylvinylstannanes: Scope and Some Mechanistic Observations" *Tetrahedron* **1995**, *51*, 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**, 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 Alkenylboronic Acids and -Trifluoroborates" *Synlett*. **1997**, 606–608.

[20] (a) Besset, T.; Poisson, T.; Pannecoucke, X. "Direct Vicinal Difunctionalization of Alkynes: An Efficient Approach towards the Synthesis of Highly Functionalized Fluorinated Alkenes" *Eur. J. Org. Chem.* **2015**, 2765–2789. (b) Bello, D.; O'Hagan, D. "Lewis Acid-Promoted Hydrofluorination of Alkynyl Sulfides to Generate α-Fluorovinyl Thioethers" *Beilstein J. Org. Chem*. **2015**, *11*, 1902–1909. (c) Nahra, F.; Patrick, S. R.; Bello, D.; Brill, M.; Obled, A.; Cordes, D. B.; Slawin, A. M. Z.; O'Hagan, D.; Nolan, S. P. "Hydrofluorination of Alkynes Catalyzed by Gold Bifluorides" *ChemCatChem* **2015**, *7*, 240–244. (d) Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. "Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and *gem*-Difluoromethylene Compounds from Alkynes" *J. Am. Chem. Soc*. **2014**, *136*, 14381–14384.

[21] (a) Akana, J. A.; Bhattacharyya, K. X.; Mueller, P.; Sadighi, J. P. "Reversible C–F Bond Formation and the Au-Catalyzed Hydrofluorination of Alkynes" *J. Am. Chem. Soc*. **2007**, *129*, 7736–7737. (b) Gorske, B. C.; Mbofana, C. T.; Miller, S. J. "Regio- and Stereoselective Synthesis of Fluoroalkenes by Directed Au(I) Catalysis" *Org. Lett*. **2009**, *11*, 4318–4321. (c) He, G.; Qiu, S.; Huang, H.; Zhu, G.; Zhang, D.; Zhang, R.;

Zhu, H. “Cu(I)- or Ag(I)-Catalyzed Regio- and Stereocontrolled *trans*-Hydrofluorination of Ynamides” *Org. Lett*. **2016**, *18*, 1856–1859.
[22] (a) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.-I.; McCarthy, J. R. “Coupling of 2-Substituted 1-Fluorovinylstannanes with Organic Halides Catalyzed by Palladium(0)/Copper(I) Iodide. A Mild and Stereospecific Method to Monofluoro Olefins” *J. Org. Chem*. **1999**, *64*, 3476–3482. (b) Wang, Z.; Gonzalez, A.; Wnuk, S. F. “Pd-Catalyzed Couplings of (α-Fluoro)vinyl Tris(trimethylsilyl)germanes” *Tetrahedron Lett*. **2005**, *46*, 5313–5316. (c) Hanamoto, T.; Kobayashi, T. *J. Org. Chem*. **2003**, *68*, 6354–6359. (d) Qiu, J.; Gyorokos, A.; Tarasow, T. M.; Guiles, J. “Grignard Cross-Coupling Amenable to Large Scale Production of α-Fluorostyryl and α-Fluorovinylthiophenes” *J. Org. Chem*. **2008**, *73*, 9775–9777. (e) Andrei, D.; Wnuk, S. F. “Synthesis of the Multisubstituted Halogenated Olefins *via* Cross-Coupling of Dihaloalkenes with Alkylzinc Bromides” *J. Org. Chem*. **2006**, *71*, 405–408. (f) Yoshida, M.; Komata, A.; Hara, S. “Stereoselective Synthesis of Fluoroalkenes *via* (*Z*)-2-Fluoroalkenyliodonium Salts” *Tetrahedron* **2006**, *62*, 8636–8645. (g) Chen, C.; Wilcoxen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. “New Methods for the Synthesis of Fluoroolefins *via* the Palladium Catalyzed Cross-Coupling Reaction of 1-Fluorovinyl Halides with Organoboranes and Organostannanes” *J. Fluorine Chem*. **2000**, *101*, 285–290. (h) Azad Hossain, M. “β-Fluoroenol Triflates: Synthesis and Some Palladium Catalyzed Reactions” *Tetrahedron Lett*. **1997**, *38*, 49–52. (i) 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*, 560–563. (j) Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S. “Stereoselective Synthesis of (*E*)-1-Fluoro-1,3-enynes” *Tetrahedron* **2001**, *57*, 7143–7148. (k) Fujino, T.; Hinoue, T.; Usuki, Y.; Satoh, T. “Synthesis of Difluorinated Enynes through Sonogashira-Type Coupling” *Org. Lett*. **2016**, *18*, 5688–5691. (l) Xu, J.; Burton, D. J. “Stereospecific Preparation of (2*E*,4*Z*)-Monofluorodienyl Esters by the Heck Reaction of high *E*/*Z* Ratio 1-Bromo-1-fluorostyrenes” *J. Fluorine Chem*. **2004**, *125*, 725–730. (m) Li, Y.; Tu, D.-H.; Gu, Y.-J.; Wang, B.; Wang, Y.-Y.; Liu, Z.-T.; Liu, Z.-W.; Lu, J. “Oxidative Heck Reaction of Fluorinated Olefins with Arylboronic Acids by Palladium Catalysis” *Eur. J. Org. Chem*. **2015**, 4340–4343. (n) Ye, Y.; Takada, T.; Buchwald, S. L. “Palladium-Catalyzed Fluorination of Cyclic Vinyl Triflates: Effect of $TESCF_3$ as an Additive” *Angew. Chem. Int. Ed.* **2016**, *55*, 15559–15563.
[23] (a) Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. “Synthesis of Heterocyclic and Carbocyclic Fluoro-olefins by Ring-Closing Metathesis” *Org. Lett*. **2003**, *5*, 3403–3406. (b) Guérin, D.; Gaumont, A.-C.; Dez, I.; Mauduit, M.; Couve-Bonnaire, S.; Pannecoucke, X. “Access to Fluorinated Lactams through Ring-Closing Metathesis of Reluctant Fluoroalkenes Promoted by Appropriate Substitution of a Double Bond” *ACS Catal*. **2014**, *4*, 2374–2378. (c) Allmendinger, T.; Angst, C.; Karfunkel, H. “Fluorinated Allylic Alcohols as Building Blocks” *J. Fluorine Chem*. **1995**, *72*, 247–253. (d) Tranel, F.; Haufe, G. “Claisen Rearrangements Based on Vinyl Fluorides” *J. Fluorine Chem*. **2004**, *125*, 1593–1608. (e) Fu, W.; Zou, G.; Zhu, M.; Hong, D.; Deng, D.; Xun, C.; Ji, B. “Stereoselective Fluorination of Methylenecyclopropanes with *N*-F Reagents: A Modular Entry to γ-Fluorohomoallylic Sulfonimides and γ-Fluorohomoallylic Amides” *J. Fluorine Chem*. **2009**, *130*, 996–1000. (f) Jiang, M.; Shi, M. “Reactions of Methylenecyclopropanes and Vinylidenecyclopropanes with *N*-Fluorodibenzenesulfonimide” *Tetrahedron* **2009**, *65*, 5222–5227. (g) Pacheco, M. C.; Gouverneur, V. “Electrophilic Fluorodesilylation of Allenylmethylsilanes: A Novel Entry to 2-Fluoro-1,3-dienes” *Org. Lett*. **2005**, *7*, 1267–1270. (h) Bo, L.; Fu, C.; Ma, S. “Study on the Selectivity in the Electrophilic Monofluorination of 2,3-Allenoates with Selectfluor™: An Efficient Synthesis of 4-Fluoro-2(5*H*)-furanones and 3-Fluoro-4-oxo-2(*E*)-alkenoates” *Org. Biomol. Chem*. **2010**, *8*, 274–281. (i) Rousee, K.; Schneider, C.; Bouillon, J.-P.; Levacher, V.; Hoarau, C.; Couve-Bonnaire, S.; Pannecoucke, X. “Copper-Catalyzed Direct C–H Fluoroalkenylation of Heteroarenes” *Org. Biomol. Chem*. **2016**, *14*, 353–357. (j) Tian, P.; Feng, C.; Loh, T.-P. “Rhodium-Catalyzed $C(sp^2)$–$C(sp^2)$ Bond Formation *via* C–H/C–F activation” *Nature Communications* **2015**, *6*, 7472pp. (k) Furuya, T. Ritter, T. “Fluorination of Boronic Acids Mediated by Silver(I) Triflate” *Org. Lett*. **2009**, *11*, 2860–2863. (l) 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*. **2016**, *55*, 11629–11632.
[24] Chamberlin, A. R.; Bloom, S. H. "Lithioalkenes from Arenesulfonylhydrazones" *Org. React*. **1990**, *39*, 1–83.
[25] (a) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. "Total Synthesis of (-)-Colombiasin A and (-)-Elisapterosin B" *Angew. Chem. Int. Ed*. **2005**, *44*, 1221–1222. (b) Zhu, C.; Cook, S. P. "A Concise Synthesis of (+)-Artemisinin" *J. Am. Chem. Soc*. **2012**, *134*, 13577–13579. (c) Granger, K.; Casaubon, R. L.; Snapper, M. L. "Concise Synthesis of Norrisolide" *Eur. J. Org. Chem*. **2012**, 2308–2311.
[26] (a) Corey, E. J.; Roberts, B. E. "Application of a Shapiro Reaction-Suzuki Coupling Sequence to the Stereoselective Synthesis of (*E*)-Trisubstituted Olefins" *Tetrahedron Lett*. **1997**, *38*, 8919–8920. (b) Fabris, F.; De Martin, A.; De Lucchi, O. "The Cyclotrimerisation of (+)-Camphor" *Tetrahedron Lett*. **1999**, *40*, 9121–9124.
[27] (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. "Vinyllithium Reagents from Arenesulfonylhydrazones" *J. Org. Chem*. **1978**, *43*, 147–154. (b) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. "Silanes in Organic Synthesis. 8. Preparation of Vinylsilanes from Ketones and Their Regiospecific Cyclopentenone Annulation" *J. Org. Chem*. **1980**, *45*, 3017–3028. (c) Mislankar, D. G.; Mugrage, B.; Darling, S. D. "Enephosphinylation" *Tetrahedron Lett*. **1981**, *22*, 4619–4622. (d) Adlington, R. M.; Barrett, A. G. M. "Recent Applications of the Shapiro Reaction" *Acc. Chem. Res*. **1983**, *16*, 55–59. (e) Rauniyar, V.; Zhai, H.; Hall, D. G. "Convenient Preparation of Cycloalkenyl Boronic Acid Pinacol Esters" *Synth. Commun*. **2008**, *38*, 3984–3995.
[28] (a) Baudoux, J.; Cahard, D. "Electrophilic Fluorination with *N*–F Reagents" *Org. React*. **2007**, *69*, 347–672.
[29] Rosiak, A.; Hoenke, C.; Christoffers, J. "Synthesis of 3-Phenyl-4-piperidones from Acetophenone by Shapiro and *aza*-Michael Reactions and Their Further Derivatization" *Eur. J. Org. Chem*. **2007**, 4376–4382.
[30] Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. "2,4,6-Tri-isopropylbenzenesulfonyl Hydrazide: A Convenient Source of Di-imide" *Tetrahedron* **1976**, *32*, 2157–2162.
[31] (a) Barnette, W. E. "*N*-Fluoro-*N*-alkylsulfonamides: Useful Reagents for the Fluorination of Carbanions" *J. Am. Chem. Soc*. **1984**, *106*, 452–454. (b) Lee, S. H.; Schwartz, J. "Stereospecific Synthesis of Alkenyl Fluorides (with Retention) *via* Organometallic Intermediates" *J. Am. Chem. Soc*. **1986**, *108*, 2445–2447.
[32] Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. "Modified Shapiro Reactions with Bismesitylmagnesium as an Efficient Base Reagent" *Org. Lett*. **2012**, *14*, 2250–2253.
[33] For the 4-piperidone trisylhydrazone, *N*-Bn and *N*-PMP protected substrates provided similar yields of fluoroalkene products.
[34] Schimmer, B. P., Funder, J. W. ACTH, Adrenal Steroids, and Pharmacology of the Adrenal Cortex. In Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. [Online]; Brunton, L. L., Chabner, B. A., Knollmann, B. C., Eds.; McGraw-Hill: New York, 2011; Chapter 42, http://www.accesspharmacy.com/content.aspx?aID=16674048 (accessed July 12, 2013).

Chapter 2 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 2

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General Information

Unless otherwise noted, reactions were performed under nitrogen atmosphere using oven-dried glassware. The Shapiro fluorination reactions were performed in the round-bottom flasks, which were sealed with three-way valves for transferring nitrogen and reagents, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Unless otherwise noted, reagents purchased from commercial sources were used without further purification. THF was dried by passage through activated alumina columns. All alkyllithium bases were titrated prior to each reaction using diphenylacetic acid as an indicator.[1] Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing with fluorescence quenching, $KMnO_4$ solution, nihydrins, or ceric ammonium molybdate solution (CAM). ^{19}F NMR yields reported in the manuscript represent an average of at least two independent runs. Isolated yields reported in the manuscript represent either the result of one purification, or of an average of two independent purifications. Yields reported in the supporting information refer to a single experiment. Proton nuclear magnetic resonance (^1H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million downfield from tetramethylsilane and are referenced to proton resonance of residual $CHCl_3$ in the NMR solvent ($CHCl_3$ = 7.27 ppm). Chemical shifts (δ) for carbon are reported in parts per million downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak ($CDCl_3$ = 77.23 ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz); chemical shifts (δ) are reported in parts per millions, and are referenced to α,α,α-trifluorotoluene (δ = –63.72 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass data were recorded on a high-resolution mass spectrometer in the ESI mode. Infrared

spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Melting points were uncorrected and measured on Thomas Hoover Capillary Melting Point apparatus.

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

Using a syringe pump, hydrazine (2.3 mL, 2.2 mmol) was added dropwise over a period of 15 min to a pre-cooled solution of 2,4,6-triisopropylbenzenesulfonyl chloride (10 g, 33 mmol) in THF (30 mL) at –10 °C (ice-salt freezing mixture). The reaction solution was warmed to 0 °C, and stirred for additional 3 h at this temperature. Water (15 mL) was added to dissolve the precipitated solids. The products were then transferred to a separation funnel. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 30 mL). The organic layers were washed with ice-cold brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure below room temperature (25 °C). Pentane was added to the solid obtained, and the mixture was sonicated at rt for 3 min until fine solids formed. The solid was collected by filtration, washed with cold pentane, and dried *in vacuo* to give **TPSH** as a colorless solid (9.6 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 2 H), 5.52 (s, 1 H), 4.16 (sept, *J* = 6.7 Hz, 2 H), 3.65 (br, 2 H), 2.92 (sept, *J* = 6.9 Hz, 1 H), 1.28 (d, *J* = 6.7 Hz, 12 H), 1.27 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 152.0, 128.9, 124.2, 34.4, 30.0, 25.1, 23.7 ppm. HRMS (ESI, *m/z*): calcd for $C_{15}H_{27}N_2O_2S$ $[M+H]^+$ 299.1793, found 299.1794.

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

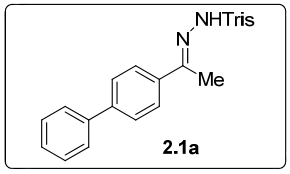
A ketone (1.0 equiv) was added to a suspension of 2,4,6-triisopropylbenzenesulfonyl hydrazide **TPSH** (> 1.0 equiv) in THF or MeOH (generally *c* = 1.0 M) at room temperature, and stirred for several hours (generally 1–5 h) under N_2. In some cases (hindered substrates), the addition of several drops of concentrated HCl or the heating facilitated the reaction.

Workup A: The reaction was quenched with a solution of aqueous $NaHCO_3$, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated to provide the crude product. The residue was triturated with MeOH (or a minimal amount

of CH_2Cl_2 and a large amount of pentane) and sonicated until white solid precipitated. The solid was filtered, washed with pentane, and dried *in vacuo*.

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

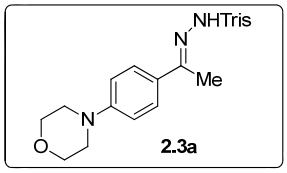
Workup C: The solvent was removed under reduced pressure, and the residue dissolved in MeOH or pentane/CH_2Cl_2, and sonicated until solids precipitated. The solid was filtered, washed with pentane and dried *in vacuo*. (In some cases, compounds were purified by column chromatography using gradient elution).



2.1a

(*E*)-*N'*-(1-([1,1'-biphenyl]-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.1a)

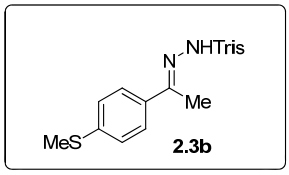
The general procedure was followed using TPSH (3.35 g, 11.2 mmol), 4-phenylacetophenone (2.00 g, 10.2 mmol), and 4 drops of HCl with THF (0.010 L) as solvent for 1.5 h at rt. Workup A (precipitation in MeOH) afforded the title compound **2.1a** as a colorless solid (4.46 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74–7.72 (m, 3 H), 7.60–7.54 (m, 4 H), 7.46–7.43 (m, 2 H), 7.38–7.34 (m, 1 H), 7.19 (s, 2 H), 4.35 (sept, *J* = 6.7 Hz, 2 H), 2.91 (sept, *J* = 6.9 Hz, 1 H), 2.22 (s, 3 H), 1.32 (d, *J* = 6.7 Hz, 12 H), 1.26 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 151.6, 150.6, 142.4, 140.5, 136.4, 131.6, 129.0, 127.8, 127.2, 127.0, 126.9, 124.0, 34.4, 30.2, 25.1, 23.7, 13.3 ppm. IR (film) 3225, 2959, 1599, 1383, 1362, 1331, 1313, 1165, 1153, 1059, 1038, 910, 841, 766, 704, 660 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{29}H_{36}N_2O_2SNa$ $[M+Na]^+$ 499.2395, found 499.2387. mp 164–165 °C.



2.3a

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

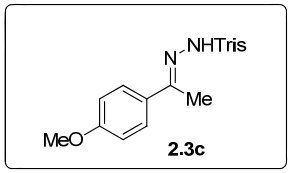
The general procedure was followed using TPSH (1.74 g, 5.84 mmol), 4-morpholinoacetophenone (1.00 g, 4.87 mmol) and 4 drops of HCl with MeOH (4.50 mL) as solvent for 6.0 h at rt. Workup B followed by chromatographic purification (CH_2Cl_2/MeOH) provided the title compound **2.3a** as a colorless solid (1.41 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J* = 9.0 Hz, 2 H), 7.42 (s, 1 H), 7.16 (s, 2 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 4.32 (sept, *J* = 6.8 Hz, 2 H), 3.85 (t, *J* = 4.8 Hz, 4 H), 3.19 (t, *J* = 4.8 Hz, 4 H), 2.89 (sept, *J* = 6.9 Hz, 1 H), 2.13 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 152.2, 151.5, 150.9, 131.8, 128.7, 127.6, 123.9, 114.6, 66.9, 48.7, 34.4, 30.2, 25.0, 23.7, 13.0 ppm. IR (film) 3180, 2959, 2864, 1603, 1518, 1425, 1377, 1331, 1306, 1232, 1167, 928, 739, 704 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{27}H_{39}N_3O_3SNa$ $[M+Na]^+$ 508.2610, found 508.2596. mp 186 °C (dec).



2.3b

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

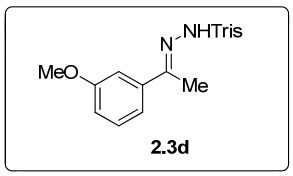
The general procedure was followed using TPSH (1.97 g, 6.62 mmol), 4-(methylthio)acetophenone (1.00 g, 6.02 mmol) with MeOH (7.00 mL) as solvent for 6.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.3b** as a light yellow solid (2.39 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, *J* = 8.0 Hz, 2 H), 7.49 (s, 1 H), 7.17 (s, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 4.30 (sept, *J* = 6.8 Hz, 2 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.48 (s, 3 H), 2.14 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5, 151.6, 150.3, 140.7, 134.2, 131.6, 126.8, 125.8, 124.0, 34.4, 30.2, 25.0, 23.7, 15.6, 13.1 ppm. IR (film) 3227, 2959, 1599, 1383, 1310, 1165, 1153, 1059, 910, 820, 770, 675 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{24}H_{34}N_2O_2S_2Na$ $[M+Na]^+$ 469.1959, found 469.1955. mp 143–144 °C.



2.3c

(*E*)-2,4,6-triisopropyl-*N'*-(1-(4-methoxyphenyl)ethylidene)benzenesulfonohydrazide (2.3c)[3]

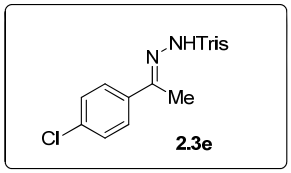
The general procedure was followed using TPSH (2.20 g, 7.33 mmol), *p*-methoxyacetophenone (1.00 g, 6.66 mmol), 2 drops of HCl with THF (0.010 L) as solvent for 5.0 h at rt. Workup A (precipitation in pentane/CH_2Cl_2) provided the title compound **2.3c** as a colorless solid (2.59 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.59 (m, 3 H), 7.17 (s, 2 H), 6.83 (d, *J*= 9.0 Hz, 2 H), 4.32 (sept, *J* = 6.8 Hz, 2 H), 3.81 (s, 3 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.15 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.9, 153.5, 151.6, 150.9, 131.7, 130.2, 127.9, 124.0, 113.7, 55.5, 34.4, 30.2, 25.0, 23.7, 13.2 ppm. HRMS (ESI, *m/z*): calcd for $C_{24}H_{34}N_2O_3SNa$ $[M+Na]^+$ 453.2188, found 453.2187.



2.3d

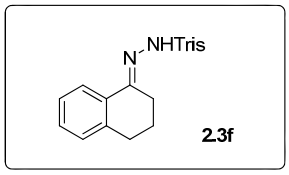
(*E*)-2,4,6-triisopropyl-*N'*-(1-(3-methoxyphenyl)ethylidene)benzenesulfonohydrazide (2.3d)

The general procedure was followed using TPSH (2.09 g, 6.99 mmol), *m*-methoxyacetophenone (1.00 g, 6.66 mmol) with MeOH (7.00 mL) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.3d** as a colorless solid (2.44 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (s, 1 H), 7.23–7.17 (m, 5 H), 6.88 (dt, *J* = 7.3, 2.0 Hz, 1 H), 4.31 (sept, *J* = 6.8 Hz, 2 H), 3.77 (s, 3 H), 2.89 (sept, *J* = 6.9 Hz, 1 H), 2.16 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 153.5, 151.5, 150.5, 139.1, 131.5, 129.3, 124.0, 119.1, 115.4, 111.8, 55.4, 34.4, 30.1, 23.7, 13.5 ppm. IR (film) 3246, 2961, 2928, 1597, 1585, 1462, 1467, 1364, 1329, 1232, 1165, 1155, 1059, 856, 785, 721, 663 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{24}H_{34}N_2O_3SNa$ $[M+Na]^+$ 453.2188, found 453.2194. mp 147–148 °C.



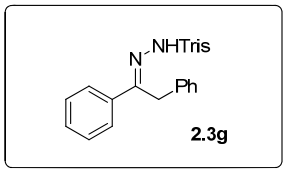
(*E*)-*N'*-(1-(4-chlorophenyl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.3e)

The general procedure was followed using TPSH (2.12 g, 7.12 mmol), 4'-chloroacetophenone (1.00 g, 6.47 mmol) with THF (6.00 mL) as solvent for 3.0 h at rt. Workup A (precipitation in pentane/CH_2Cl_2) provided the title compound **2.3e** as a colorless solid (0.900 g, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (br, 1 H), 7.57 (dd, *J* = 1.9, 6.8 Hz, 2 H), 7.28 (dd, *J* = 6.8, 1.9 Hz, 2 H), 7.18 (s, 2 H), 4.30 (sept, *J* = 6.8 Hz, 2 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.15 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7, 151.6, 149.5, 136.1, 135.6, 131.5, 128.6, 127.7, 124.0, 34.4, 30.2, 25.0, 23.7, 13.3 ppm. IR (film) 3244, 2961, 2926, 1599, 1462, 1383, 1362, 1331, 1306, 1265, 1165, 1099, 908, 831, 739, 679 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{23}H_{31}ClN_2O_2SNa$ $[M+Na]^+$ 457.1692, found 457.1689. mp 150–151 °C.



(*E*)-*N'*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.3f)[4]

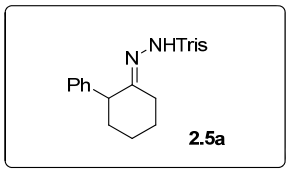
The general procedure was followed using TPSH (2.24 g, 7.52 mmol), alpha-tetralone (1.00 g, 6.84 mmol) with MeOH (7.00 mL) as solvent for 5.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.3f** as a colorless solid (1.40 g, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.50 (s, 1 H), 7.23 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1 H), 7.17 (s, 2 H), 7.16–7.09 (m, 2 H), 4.32 (sept, *J* = 6.8 Hz, 2 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.74 (t, *J* = 6.0 Hz, 2 H), 2.46 (t, *J* = 6.6 Hz, 2 H), 1.97–1.90 (m, 2 H), 1.32 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 151.6, 150.8, 139.7, 132.0, 131.8, 129.4, 128.5, 126.3, 125.3, 123.9, 34.3, 30.2, 29.5, 25.5, 25.0, 23.7, 21.6 ppm. HRMS (ESI, *m/z*): calcd for $C_{25}H_{34}N_2O_2SNa$ $[M+Na]^+$ 449.2239, found 449.2237.



2.3g

(*E*)-*N'*-(1,2-diphenylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.3g)[5]

The general procedure was followed using TPSH (1.67 g, 5.60 mmol), deoxybenzoin (1.00 g, 5.09 mmol), 4 drops of HCl with THF (0.010 L) as solvent for 1.5 h at rt. Workup A (precipitation in pentane/CH_2Cl_2) provided the title compound **2.3g** as a colorless solid (1.14 g, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 8.0 Hz, 2 H), 7.59 (s, 1 H), 7.35–7.27 (m, 6 H), 7.18–7.15 (m, 4 H), 4.13 (sept, *J* = 6.8 Hz, 2 H), 4.06 (s, 2 H), 2.90 (sept, *J* = 7.0 Hz, 1 H), 1.25 (d, *J* = 7.0 Hz, 6 H), 1.23 (d, *J* = 6.8 Hz, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 152.9, 151.8, 137.3, 134.1, 131.6, 129.8, 129.7, 128.5, 128.1, 127.6, 126.8, 124.0, 34.4, 33.6, 30.4, 25.1, 23.7 ppm. HRMS (ESI, *m/z*): calcd for $C_{29}H_{36}N_2O_2SNa$ $[M+Na]^+$ 499.2395, found 499.2392.

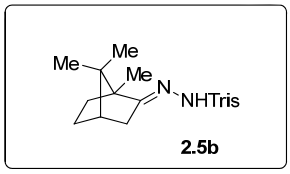


2.5a

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

The general procedure was followed using TPSH (1.72 g, 5.76 mmol), 2-phenylcyclohexanone (1.00 g, 5.74 mmol), 4 drops of HCl with MeOH (6.00 mL) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.5a** as a colorless solid (2.09 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1 H), 7.18 (s, 2 H), 7.12–7.05 (m, 3 H), 6.87 (d, *J* = 6.5 Hz, 2 H), 4.18 (sept, *J* = 6.7 Hz, 2 H), 3.60 (t, *J* = 5.0 Hz, 1 H), 2.95 (sept, *J* = 6.9 Hz, 1 H), 2.35–2.24 (m, 2 H), 2.00–1.88 (m, 2 H), 1.78–1.60 (m, 4 H), 1.30 (dd, *J* = 6.9, 2.1 Hz, 6 H), 1.21 (d, *J* = 6.7 Hz, 6 H), 1.18 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2, 153.2, 151.4, 140.2, 131.7, 128.3, 127.6, 126.2, 123.8, 47.9, 34.4, 30.8, 29.9, 25.9, 24.9, 23.8, 22.5 ppm. IR (film) 3232, 2955, 2359, 1643, 1599, 1427, 1393, 1327, 1263, 1167,

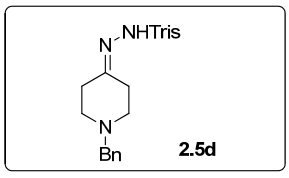
1009, 926, 883, 729, 702, 669 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{27}H_{39}N_2O_2S$ $[M+H]^+$ 455.2732, found 455.2747. mp 130–131 °C.



2.5b

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

The general procedure was followed using TPSH (2.16 g, 7.23 mmol), camphor (1.00 g, 6.57 mmol), 2 drops of HCl with acetonitrile (0.010 L) as solvent for 6.0 h at rt. Workup C (precipitation in pentane/CH_2Cl_2) provided the title compound **2.5b** as a colorless solid (0.860 g, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (s, 2 H), 6.97 (br, 1 H), 4.21 (sept, *J* = 6.8 Hz, 2 H), 2.91 (sept, *J* = 6.9 Hz, 1 H), 2.23 (dt, *J* = 16.6, 3.6 Hz, 1 H), 1.96 (t, *J* = 4.4 Hz, 1 H), 1.85–1.78 (m, 1 H), 1.73 (d, *J* = 16.7 Hz, 1 H), 1.63 (td, *J* = 12.2, 4.2, 1 H), 1.28–1.25 (m, 19 H), 1.17–1.10 (m, 1 H), 0.87 (d, *J* = 1.5 Hz, 6 H), 0.62 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 153.1, 151.5, 131.7, 123.7, 53.0, 48.1, 44.2, 34.3, 33.8, 32.5, 30.0, 27.4, 25.0, 23.7, 19.5, 18.8, 11.1 ppm. HRMS (ESI, *m/z*): calcd for $C_{25}H_{40}N_2O_2SNa$ $[M+Na]^+$ 455.2708, found 455.2692.



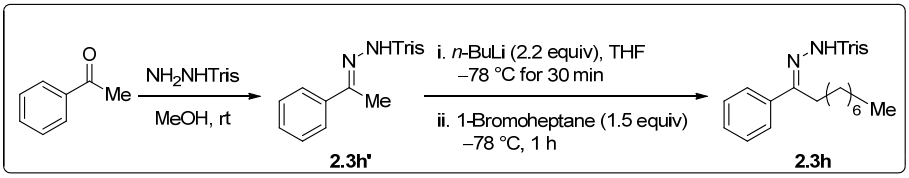
2.5d

***N'*-(1-benzylpiperidin-4-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5d)**

The general procedure was followed using TPSH (0.870 g, 2.90 mmol), *N*-benzyl-4-piperidone (0.500 g, 2.64 mmol) and 2 drops of HCl with THF (3.00 mL) as solvent for 3.5 h at rt. Workup B followed by chromatographic purification (CH_2Cl_2/MeOH) provided the title compound **2.5d** as a colorless solid (0.800 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (br, 1 H), 7.30–7.22 (m, 5 H), 7.15 (s, 2 H), 4.24 (sept, *J* = 6.7 Hz, 2 H), 3.48 (s, 2 H), 2.89 (sept, *J* = 6.9 Hz, 1 H), 2.50 (t, *J* = 5.7 Hz, 2 H), 2.46 (t, *J* = 5.7 Hz, 2

H), 2.36–2.31 (m, 4 H), 1.24 (d, J = 6.6 Hz, 18 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.9, 153.1, 151.4, 138.2, 131.6, 129.0, 128.4, 127.3, 123.8, 62.4, 53.5, 52.0, 34.6, 34.2, 29.9, 26.7, 24.9, 23.7 ppm. IR (film) 3236, 2959, 2868, 1599, 1458, 1425, 1364, 1319, 1165, 1151, 1032, 739, 698, 660 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{27}H_{39}N_3O_2SNa$ $[M+Na]^+$ 492.2661, found 492.2638. mp 136–138 °C.

Preparation of Trisyl Hydrazone 2.3h



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

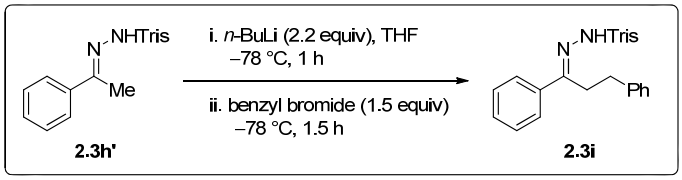
The general procedure was followed using TPSH (5.96 g, 20.0 mmol), acetophenone (2.00 g, 16.7 mmol) with MeOH (0.020 L) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.3h'** as a colorless solid (4.75 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (br, 1 H), 7.66–7.63 (m, 2 H), 7.34–7.29 (m, 3 H), 7.18 (s, 2 H), 4.33 (sept, J = 6.8 Hz, 2 H), 2.90 (sept, J = 6.9 Hz, 1 H), 2.18 (s, 3 H), 1.31 (d, J = 6.8 Hz, 12 H), 1.25 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 151.6, 150.9, 137.6, 131.6, 129.6, 128.4, 126.5, 124.0, 34.4, 30.2, 25.0, 23.7, 13.3 ppm. HRMS (ESI, *m/z*): calcd for $C_{23}H_{32}N_2O_2SNa$ $[M+Na]^+$ 423.2082, found 423.2086.

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

n-BuLi (2.26 ml, 5.50 mmol) was added dropwise *via* syringe pump over a period of 15 min to a cooled solution of **2.3h'** (1.00 g, 2.50 mmol) in THF (12.5 mL) at –78 °C. The reaction solution was stirred at –78 °C for 30 min, and then 1-bromoheptane (0.590 ml, 3.75 mmol) was added dropwise to the solution over a period of 5 min at –78 °C. The resulting solution was stirred at –78 °C for 1 h. Water was added at –78 °C, and then the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (2 x 0.015 L), and combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound **2.3h** as a colorless solid (1.50 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65–7.62 (m,

3 H), 7.34–7.28 (m, 3 H), 7.17 (s, 2 H), 4.29 (sept, *J* = 6.8 Hz, 2 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.57 (t, *J* = 7.9 Hz, 2 H), 1.56–1.49 (m, 2 H), 1.44–1.36 (m, 2 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H), 1.36–1.24 (m, 8 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 153.5, 151.7, 136.9, 131.6, 129.7, 129.5, 128.4, 127.1, 126.6, 124.0, 123.9, 38.4, 34.4, 32.0, 30.2, 29.5, 29.3, 27.0, 26.0, 25.1, 23.7, 22.8, 21.4 ppm. IR (film) 3196, 2957, 2928, 1599, 1464, 1383, 1317, 1165, 1153, 941, 922, 764, 692, 662 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{30}H_{46}N_2O_2SNa$ $[M+Na]^+$ 521.3178, found 521.3162. mp 97–98 °C.

Preparation of Trisyl Hydrazone 2.3i

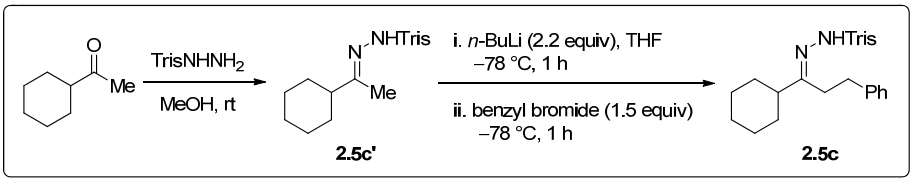


(*E*)-*N'*-(1,3-diphenylpropylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.3i)

n-BuLi (3.40 ml, 8.18 mmol) was added dropwise to a solution of **2.3h'** (1.49 g, 3.72 mmol) in THF (20.0 mL) over a period of 15 min at –78 °C *via* syringe pump. The reaction solution was stirred at –78 °C for 1 h, and then benzyl bromide (0.670 ml, 5.58 mmol) was added dropwise to the solution over a period of 5 min at –78 °C. The resulting solution was stirred at –78 °C for 1.5 h, water was added at –78 °C, and then the solution was recovered to rt. The aqueous layer was extracted with EtOAc (2 x 0.015 L), and combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound **2.3i** as a colorless solid (1.25 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.65 (m, 2 H), 7.47 (s, 1 H), 7.37–7.28 (m, 6 H), 7.24–7.22 (m, 2 H), 7.17 (s, 2 H), 4.30 (sept, *J* = 6.8 Hz, 2 H), 2.93–2.82 (m, 5 H), 1.30 (d, *J* = 6.8 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5, 151.8, 140.3, 136.6, 131.4, 129.6, 129.0, 128.5, 128.4, 126.9, 126.6, 124.0, 34.4, 31.8, 30.2, 29.0, 25.1, 23.7 ppm. IR (film) 3233, 2961, 2928, 1599, 1458, 1425, 1383, 1315, 1165, 1153, 1036, 916, 740, 694,

660 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{30}H_{38}N_2O_2SNa$ $[M+Na]^+$ 513.2552, found 513.2540. mp 155–157 °C.

Preparation of Trisyl Hydrazone 2.5c



(*E*)-*N'*-(1-cyclohexylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5c')[7]

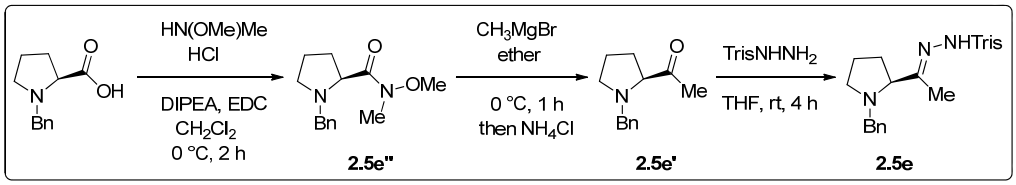
The general procedure was followed using TPSH (1.28 g, 4.29 mmol), 1-cyclohexylethanone (0.540 g, 4.29 mmol with MeOH (4.00 mL) as solvent for 5.0 h at rt. Workup C (precipitation in MeOH) provided the title compound **2.5c'** as a colorless solid (1.33 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (s, 3 H), 4.21 (sept, *J* = 6.7 Hz, 2 H), 2.91 (sept, *J* = 6.9 Hz, 1 H), 2.10–2.05 (m, 1 H), 1.73 (s, 3 H), 1.67–1.59 (m, 5 H), 1.28–1.25 (m, 18 H), 1.22–1.08 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 153.2, 151.4, 131.8, 123.7, 46.8, 34.3, 30.0, 26.2, 26.0, 25.0, 23.7, 14.0 ppm. HRMS (ESI, *m/z*): calcd for $C_{23}H_{42}N_3O_2S$ $[M+NH_4]^+$ 424.2998, found 424.2990.

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

n-BuLi (0.480 ml, 1.08 mmol) was added dropwise to a solution of **2.5c'** (0.200 g, 0.490 mmol) in THF (2.50 mL) over a period of 5 min at –78 °C *via* syringe pump. The reaction solution was stirred at –78 °C for 1 h, and then benzyl bromide (0.090 ml, 0.735 mmol) was added dropwise to the solution over a period of 2 min at –78 °C. The resulting solution was stirred at –78 °C for 1 h. Water was added at –78 °C, and then the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (2 x 0.003 L), and combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound **2.5c** as a colorless solid (0.155 g, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.31 (m, 2 H), 7.25–7.23 (m, 1 H), 7.20–7.14 (m, 5 H), 4.19 (sept, *J* = 6.7 Hz, 2 H), 2.92 (sept, *J* = 6.9 Hz, 1 H), 2.78–2.74 (m, 2 H), 2.43–2.39 (m, 2 H), 2.01 (br, 1 H), 1.67–1.60 (m, 5 H), 1.27 (d, *J* = 6.7 Hz, 12 H), 1.26 (d,

J = 6.9 Hz, 6 H), 1.19–1.11 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 153.3, 151.6, 140.5, 131.7, 128.9, 128.3, 126.8, 123.7, 45.8, 34.4, 31.2, 30.6, 30.5, 30.1, 26.2, 25.1, 23.8 ppm. IR (film) 3236, 2959, 2928, 2866, 1601, 1454, 1383, 1323, 1163, 1153, 941, 881, 746, 700, 660 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{30}H_{44}N_2O_2SNa$ $[M+Na]^+$ 519.3021, found 519.3018. mp 135–136 °C.

Preparation of Trisyl Hydrazone 2.5e



(*S*)-1-benzyl-*N*-methoxy-*N*-methylpyrrolidine-2-carboxamide (2.5e″)

(*L*)–*N*-Benzyl–proline (2.98 g, 15.5 mmol) was suspended in CH_2Cl_2 (0.070 L), and HN(OMe)Me•HCl (1.42 g, 14.5 mmol), diisopropylethylamine (2.40 mL, 14.5 mmol) and EDCI (2.78 g, 14.5 mmol) were added into the reaction mixture sequentially at 0 °C. The resulting reaction solution was stirred at 0 °C for 2 h, and then water was added to quench the reaction. The organic layer was collected, and the aqueous layer was extracted further with CH_2Cl_2 (2 x 0.030 L). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by column chromatography using gradient MeOH in CH_2Cl_2 (2% to 5%) for elution to offer **2.5e″** as a liquid (1.41 g, 39%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.22 (m, 5 H), 3.94 (d, *J* = 12.8 Hz, 1 H), 3.57–3.56 (m, 4 H), 3.55 (d, *J* = 12.8 Hz, 1 H), 3.17 (s, 3 H), 3.13–3.08 (m, 1 H), 2.44 (q, *J* = 8.2 Hz, 1 H), 2.19–2.10 (m, 1 H), 1.96–1.75 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 138.5, 129.4, 128.1, 127.0, 62.0, 61.2, 58.0, 53.0, 32.4, 29.1, 23.0 ppm. IR (film) 2964, 2939, 2874, 2359, 2341, 1663, 1454, 1387, 1312, 1177, 999, 745, 700 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$ 249.1603, found 249.1591.

(*S*)-1-(1-benzylpyrrolidin-2-yl)ethanone (2.5e')[8]

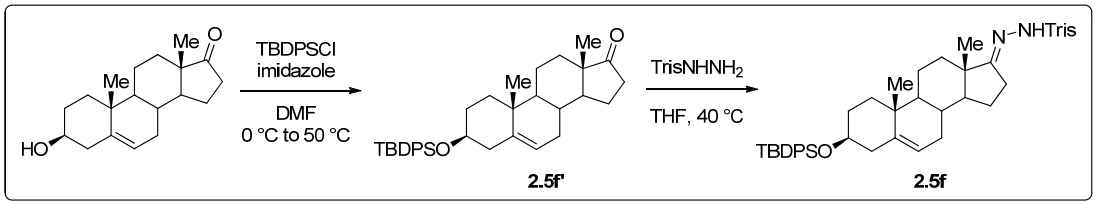
2.5e″ (1.34 g, 5.40 mmol) was dissolved in dry ether (0.050 L) and cooled to 0 °C. Methylmagnesium bromide (2.52 mL, 7.56 mmol) was added dropwise into the solution over 10 min at 0 °C. The solution was stirred at this temperature for 1 h and quenched with NH_4Cl (sat'd). The organic layer was collected

and the aqueous layer was extracted further with EtOAc (2 x 0.025 L). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by column chromatography using gradient MeOH in CH_2Cl_2 (2% to 4%) for elution to offer **2.5e'** as a liquid (0.930 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.24 (m, 5 H), 3.82 (d, *J* = 13.0 Hz, 1 H), 3.45 (d, *J* = 13.0 Hz, 1 H), 3.13–3.07 (m, 2 H), 2.33–2.27 (m, 1 H), 2.15 (s, 3 H), 2.13–2.06 (m, 1 H), 1.90–1.76 (m, 3 H) ppm. HRMS (ESI, *m/z*): calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1388, found 204.1392.

(*S*,*E*)-*N'*-(1-(1-benzylpyrrolidin-2-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5e)

The general procedure was followed using TPSH (1.39 g, 4.65 mmol), **2.5e'** (0.860 g, 4.23 mmol) with THF (4.5 mL) as solvent for 4.0 h at rt. Workup B followed by chromatographic purification (CH_2Cl_2/MeOH) provided the title compound **2.5e** as a colorless solid (1.79 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (s, 1 H), 7.23–7.18 (m, 3 H), 7.14 (s, 2 H), 7.06 (dd, *J* = 7.6, 2.1 Hz, 2 H), 4.26 (sept, *J* = 6.7 Hz, 2 H), 3.44 (d, *J* = 13.4 Hz, 1 H), 3.04–3.01 (m, 2 H), 2.93–2.88 (m, 1 H), 2.84 (sept, *J* = 6.9 Hz, 1 H), 2.12 (q, *J* = 8.4 Hz, 1 H), 1.92–1.82 (m, 1 H), 1.76 (s, 3 H), 1.75–1.61 (m, 3 H), 1.30 (d, *J* = 6.7 Hz, 6 H), 1.25 (d, *J* = 6.8 Hz, 6 H), 1.18 (t, *J* = 6.7 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 153.3, 151.4, 138.9, 131.5, 129.0, 128.2, 126.9, 123.8, 69.6, 57.6, 53.2, 34.3, 30.0, 28.7, 25.1, 25.0, 23.6, 23.3, 10.7 ppm. IR (film) 3231, 2959, 2868, 2359, 2341, 1599, 1458, 1425, 1383, 1364, 1323, 1165, 1153, 1038, 912, 739, 698, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{28}H_{41}N_3O_2SNa$ $[M+Na]^+$ 506.2817, found 506.2793. mp 134–135 °C.

Preparation of Trisyl Hydrazone 2.5f



(3*S*,10*R*,13*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-10,13-dimethyl-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-1*H*-cyclopenta[a]phenanthren-17(2*H*)-one (2.5f')[9]

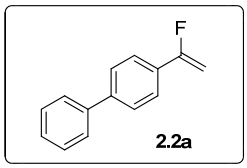
(+)-Dehydroepiandrosterone (0.300 g, 1.04 mmol) was dissolved in dry DMF (0.010 L) at rt, and then imidazole (177 mg, 2.60 mmol) was added at 0 °C. The resulting solution was stirred at 0 °C for 15 min, and then TBDPSCl (0.540 mL, 2.08 mmol) was added dropwise. The solution was stirred at 50 °C overnight. A solution of saturated NH_4Cl (5.0 mL) was added at rt and stirred for additional 30 min. DMF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layer was dried over anhydrous $NaSO_4$, concentrated and purified by column chromatography using gradient elution (EtOAc/hexanes) to furnish **2.5f'** as a colorless foam (500 mg, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.68 (m, 4 H), 7.42–7.38 (m, 6 H), 5.17 (d, *J* = 5.3 Hz, 1 H), 3.59–3.52 (m, 1 H), 1.48–2.45 (m, 17 H), 1.27–1.19 (m, 2 H), 1.08 (s, 9 H), 1.03 (s, 3 H), 0.87 (s, 3 H) ppm. HRMS (ESI, *m/z*): calcd for $C_{35}H_{47}O_2Si$ $[M+H]^+$ 527.3345, found 527.3337.

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

The general procedure was followed using TPSH (401 mg, 1.34 mmol), **2.5f'** (590 mg, 1.12 mmol) with THF (1.0 mL) as solvent for 6.0 h at 40 °C. Workup C followed by chromatographic purification (EtOAc / hexanes) provided the title compound **2.5f** as a colorless solid (230 mg, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 7.15 (s, 2 H), 6.92 (s, 1 H), 5.12–5.11 (m, 1 H), 4.19 (sept, *J* = 6.7 Hz, 2 H), 3.54–3.48 (m, 1 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 2.19–2.35 (m, 2 H), 2.04–2.15 (m, 2 H), 1.94–1.96 (m, 1 H), 1.76–1.86 (m, 2 H), 1.69–1.36 (m, 8 H), 1.27–1.24 (m, 19 H), 1.06–0.97 (m, 13 H), 0.86–0.80 (m, 2 H), 0.73 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.8, 153.2, 151.5, 141.7, 136.0, 135.0, 131.7, 129.7, 127.7, 123.7, 120.6, 73.3, 53.9, 50.4, 44.8, 42.6, 37.3, 36.8, 34.3, 33.8, 32.0, 31.5, 31.4, 30.1, 27.2, 26.0, 25.1, 25.0, 23.8, 23.6, 20.6, 19.6, 19.3, 16.8 ppm. IR (film) 3441, 2959, 2932, 2359, 1653, 1636, 1427, 1381, 1325, 1165, 1153, 1109, 1086, 741, 702, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{50}H_{74}N_3O_3SSi$ $[M+NH_4]^+$ 824.5220, found 824.5190. mp 117–118 °C.

General Procedure for the Shapiro Fluorination of Trisyl Hydrazones 2.1a, 2.3a–i, 2.5a–f

An oven-dried round bottom flask was charged with the trisylhydrazone **2.1a**, **2.3a–i**, and **2.5a–f** (1.0 equiv) and a magnetic stir bar. The reaction vessel was equipped with a three-way valve, evacuated and backfilled with nitrogen. Dry THF (*c* = 0.20 M) was added and the mixture was stirred at room temperature until the trisylhydrazone dissolved. The solution was cooled to –78 °C, and then base (2.2 equiv) was added dropwise to the stirred solution. The resulting solution was stirred at –78 °C for 30 min to generate the dianion, and then at 0 °C for 20 min to release N_2. Subsequently, the reaction was cooled to –78 °C, and then a solution of NFSI (1.5 equiv, *c* = 0.49 ~ 0.5 M in THF) was added dropwise over 2 min. Additional THF (0.1 mL) was used to wash the vial, and added successively. The resulting solution was stirred at –78 °C for 30 min, and then at rt for 2 h. A 1 N solution of α,α,α-trifluorotoluene in EtOAc (100 μL, 0.10 mmol) was added as an internal standard, and the resulting mixture was stirred at rt for 5 min. After standing for 3 min, an aliquot of the upper clear solution was removed and subjected to ^{19}F NMR analysis to determine the yield of fluoroalkene **2.2a**, **2.4a–i**, and **2.6a–f.** After the ^{19}F NMR analysis, the NRM sample was returned to the bulk of the reaction mixture, and the combined mixture was concentrated under reduced pressure. The resulting residue was added to a solution of $NaHCO_3$ (1.0 mL), stirred, and extracted with ether (3 x 5 mL). (In some cases, EtOAc was used for extraction.) The organic layers were dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography provided the desired product.

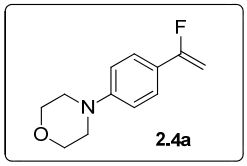


2.2a

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

The general procedure was followed using **2.1a** (119 mg, 0.250 mmol), *n*-BuLi (0.240 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.2a** as a colorless solid (38.4 mg, 75%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.62 (m, 6 H),

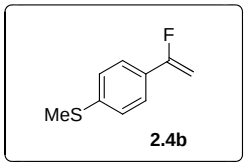
7.50–7.46 (m, 2 H), 7.41–7.38 (m, 1 H), 5.10 (dd, *J* = 49.7, 3.5 Hz, 1 H), 4.90 (dd, *J* = 17.8, 3.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163 (d, *J* = 248.5 Hz), 142.3, 140.5, 131.1 (*J* = 29.3 Hz), 129.1, 127.9, 127.4, 127.2, 125.3 (*J* = 6.9 Hz), 89.8 (*J* = 22.3 Hz) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.9 (dd, $^3J_{F–H}$ = 49.6, 18.1 Hz, 1 F) ppm. IR (film) 2359, 2341, 1647, 1404, 1292, 928, 843, 766, 689 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{14}H_{11}FNa$ $[M+Na]^+$ 221.0742, found 221.0748. mp 120–121 °C.



2.4a

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

The general procedure was followed using **2.3a** (121 mg, 0.250 mmol), *n*-BuLi (0.240 mL, 0.550 mmol), and NFSI (86.7 mg, 0.275 mmol). Workup and chromatographic purification (2% EtOAc in hexanes) provided the title compound **2.4a** as a colorless solid (35.0 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 4.87 (dd, *J* = 50.4, 3.4 Hz, 1 H), 4.71 (dd, *J* = 18.2, 3.4 Hz, 1 H), 3.87 (t, *J* = 4.9 Hz, 4 H), 3.22 (t, *J* = 4.9 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3 (d, *J* = 247.1 Hz), 152.0, 125.9 (d, *J* = 7.0 Hz), 123.4 (d, *J* = 29.8 Hz), 114.9 (d, *J* = 1.5 Hz), 87.2 (d, *J* = 22.8 Hz), 66.9, 48.8 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.7 (dd, $^3J_{F–H}$ = 50.4, 18.1 Hz, 1 F) ppm. IR (film) 2856, 2359, 1645, 1518, 1279, 1265, 1123, 920, 849, 822 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{15}FNO$ $[M+H]^+$ 208.1138, found 208.1129. mp 111–112 °C.

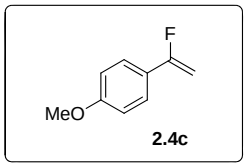


2.4b

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

The general procedure was followed using **2.3b** (223 mg, 0.500 mmol), *n*-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4b** as a light yellow solid (60.0 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, *J* = 8.4 Hz,

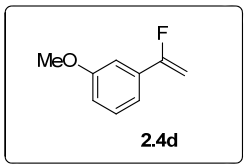
2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 4.99 (dd, *J* = 49.9, 3.5 Hz, 1 H), 4.82 (dd, *J* = 17.9, 3.5 Hz, 1 H), 2.51 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.8 (d, *J* = 248 Hz), 140.6, 128.8 (d, *J* = 29.6 Hz), 126.1 (d, *J* = 1.5 Hz), 125.1 (d, *J* = 7.0 Hz), 89.1 (d, *J*= 22.6 Hz), 15.6 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.1 (dd, $^3J_{F–H}$ = 50.0, 18.1 Hz, 1 F) ppm. IR (film) 2922, 2361, 1647, 1493, 1396, 1288, 1107, 922, 821, 739 cm^{-1}. HRMS (ESI, *m/z*): calcd for C_9H_9FSNa $[M+Na]^+$ 191.0307, found 191.0316. mp 48–49 °C.



2.4c

1-(1-fluorovinyl)-4-methoxybenzene (2.4c)[10]

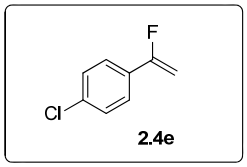
The general procedure was followed using **2.3c** (215 mg, 0.500 mmol), *n*-BuLi (0.490 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4c** as a colorless liquid (41.0 mg, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 4.89 (dd, *J* = 50.2, 3.4 Hz, 1 H), 4.74 (dd, *J* = 18.1, 3.4 Hz, 1 H), 3.84 (s, 3 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.2 (dd, $^3J_{F–H}$ = 50.0, 18.1 Hz, 1 F) ppm. HRMS (ESI, *m/z*): calcd for $C_9H_{13}FON$ $[M+NH_4]^+$ 170.0981, found 170.0977.



2.4d

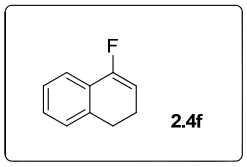
1-(1-fluorovinyl)-3-methoxybenzene (2.4d)[11]

The general procedure was followed using **2.3d** (86.1 mg, 0.200 mmol), *n*-BuLi (0.220 mL, 0.500 mmol), and NFSI (110 mg, 0.350 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4d** as a colorless liquid (13.0 mg, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.28 (m, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.10–7.09 (m, 1 H), 6.92 (dd, *J* = 8.2, 2.6 Hz, 1 H), 5.04 (dd, *J* = 49.6, 3.5 Hz, 1 H), 4.87 (dd, *J* = 17.8, 3.5 Hz, 1 H), 3.84 (s, 3 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (dd, $^3J_{F–H}$ = 49.6, 18.1 Hz, 1 F) ppm. HRMS (ESI, *m/z*): calcd for $C_9H_{10}FO$ $[M+H]^+$ 153.0716, found 153.0720.



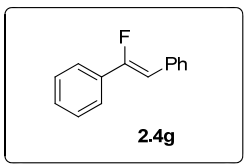
1-chloro-4-(1-fluorovinyl)benzene (2.4e)[12]

The general procedure was followed using **2.3e** (218 mg, 0.500 mmol), *n*-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4e** as a colorless liquid (60.0 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 8.7 Hz, 2 H), 5.03 (dd, *J* = 49.4, 3.6 Hz, 1 H), 4.89 (dd, *J* = 17.8, 3.6 Hz, 1 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.9 (dd, $^{3}J_{F–H}$ = 49.3, 17.7 Hz, 1 F) ppm. HRMS (ESI, *m/z*): calcd for C_8H_6ClFNa $[M+Na]^+$ 179.0040, found 179.0032.



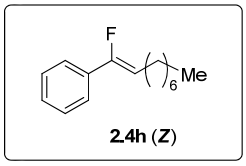
4-fluoro-1,2-dihydronaphthalene (2.4f)[13]

The general procedure was followed using **2.3f** (213 mg, 0.500 mmol), *n*-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4f** as a colorless liquid (37.0 mg, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.37 (m, 1 H), 7.26–7.20 (m, 2 H), 7.17–7.15 (m, 1 H), 5.49 (dt, *J* = 14.0, 4.6 Hz, 1 H), 2.84 (t, *J* = 8.1 Hz, 2 H), 2.44–2.37 (m, 2 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –127.0 (ddt, $^{3}J_{F–H}$ = 13.9 Hz, $^{4}J_{F–H}$ = 5.1, 2.1 Hz, 1 F) ppm. HRMS (ESI, *m/z*): calcd for $C_{10}H_9FNa$ $[M+Na]^+$ 171.0586, found 171.0593.



(*Z*)-(1-fluoroethene-1,2-diyl)dibenzene (2.4g)[14]

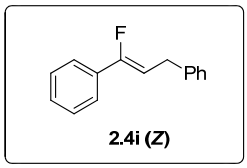
The general procedure was followed using **2.3g** (238 mg, 0.500 mmol), *s*-BuLi (1.00 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4g** as a colorless solid (82.3 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.67 (m, 4 H), 7.46–7.37 (m, 5 H), 7.31–7.27 (m, 1 H), 6.34 (d, J = 39.5 Hz, 1 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –114.2 (d, $^{3}J_{F–H}$ = 39.9 Hz, 1 F) ppm. HRMS (ESI, *m/z*): calcd for $C_{14}H_{11}FNa$ $[M+Na]^+$ 221.0742, found 221.0749.



2.4h (*Z*)

(*Z*)-(1-fluoronon-1-en-1-yl)benzene (2.4h)[15]

The general procedure was followed using **2.3h** (249 mg, 0.500 mmol), *n*-BuLi (0.45 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4h** as a colorless liquid (85.3 mg, 77%).[16] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52–7.50 (m, 2 H), 7.38–7.28 (m, 3 H), 5.41 (dt, J = 37.6, 7.6 Hz, 1 H), 2.32–2.26 (m, 2 H), 1.50–1.23 (m, 10 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –121.5 (d, $^{3}J_{F–H\ (trans)}$ = 37.2 Hz, 1 F, *Z* isomer), –102.8 (d, $^{3}J_{F–H\ (cis)}$ = 22.9 Hz, 1 F, *E* isomer) ppm. HRMS (ESI, *m/z*): calcd for $C_{15}H_{21}FNa$ $[M+Na]^+$ 243.1525, found 243.1531.

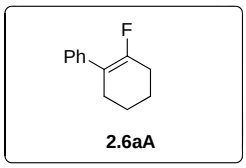


2.4i (*Z*)

(*Z*)-(1-fluoroprop-1-ene-1,3-diyl)dibenzene (2.4i)[17]

The general procedure was followed using **2.3i** (245 mg, 0.500 mmol), *n*-BuLi (0.49 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound **2.4i** as a colorless liquid (46.0 mg, 43%).[16] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.22 (m, 10 H), 5.61 (dt, J = 36.3, 7.7 Hz, 1 H), 3.66 (dd, J = 7.7, 1.4 Hz, 2 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –

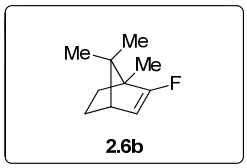
121.0 (d, $^{3}J_{F–H\ (trans)}$ = 36.5 Hz, 1 F, *Z* isomer), –100.1 (d, $^{3}J_{F–H\ (cis)}$ = 21.4 Hz, 1 F, *E* isomer) ppm. HRMS (ESI, *m/z*): calcd for $C_{15}H_{13}FNa$ $[M+Na]^{+}$ 235.0899, found 235.0891.



2.6aA

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

The general procedure was followed using **2.5a** (114 mg, 0.250 mmol), *t*-BuLi (0.400 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided compound **2.6aA** as a colorless liquid (29.0 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.41 (m, 2 H), 7.37–7.32 (m, 2 H), 7.26–7.21 (m, 1 H), 2.46–2.40 (m, 2 H), 2.39–2.34 (m, 2 H), 1.87–1.80 (m, 2 H), 1.78–1.71 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8 (d, *J* = 257 Hz), 137.8, 128.2, 127.9 (d, *J* = 4.3 Hz), 126.8, 113.7 (d, *J* = 6.9 Hz), 28.4 (d, *J* = 4.4 Hz), 26.7 (d, *J* = 23.9 Hz), 23.0 (d, *J* = 9.5 Hz), 22.9 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.0 (s, 1 F) ppm. IR (film) 2934, 1686, 1493, 1445, 1360, 1117, 760, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{14}F$ $[M+H]^{+}$ 177.1080, found 177.1078.

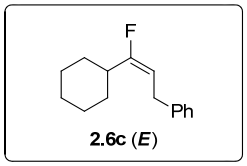


2.6b

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

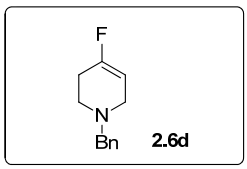
The general procedure was followed using **2.5b** (433 mg, 1.00 mmol), *s*-BuLi (1.64 mL, 2.20 mmol), and NFSI (473 mg, 1.50 mmol). Workup and chromatographic purification (pentane) provided compound **2.6b** as a colorless liquid (68.0 mg, 44%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96 (d, *J* = 3.6 Hz, 1 H), 2.32–2.28 (m, 1 H), 1.91–1.85 (m, 1 H), 1.64–1.59 (m, 1 H), 1.34–1.29 (m, 1 H), 1.16–1.11 (m, 1 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.76 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4 (d, *J* = 293.6 Hz), 103.2 (d, *J* = 2.1 Hz), 56.3 (d, *J* = 3.6 Hz), 52.2 (d, *J* = 17.6 Hz), 49.0 (d, *J* = 6.0 Hz), 31.5 (d, *J* = 4.1 Hz), 26.7 (d, *J* =

3.5 Hz), 20.0, 19.6, 9.3 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.7 (s, 1 F) ppm. HRMS (ESI, *m/z*): calcd for $C_{10}H_{15}FNa$ $[M+Na]^+$ 177.1055, found 177.1053.



(*E*)-(3-cyclohexyl-3-fluoroallyl)benzene (2.6c)

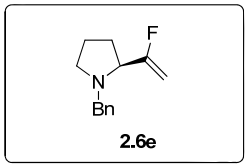
The general procedure was followed using **2.5c** (124 mg, 0.250 mmol), *n*-BuLi (0.240 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided compound **2.6c** *(E)* as a colorless liquid (25.0 mg, 46%).[16] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.29 (m, 2 H), 7.24–7.19 (m, 3 H), 5.12 (dt, *J* = 22.000, 8.2 Hz, 1 H), 3.33 (d, *J* = 8.2 Hz, 2 H), 2.51 (dtt, *J* = 30.8, 11.9, 3.4 Hz, 1 H), 1.84–1.80 (m, 2 H), 1.74–1.70 (m, 3 H), 1.59–1.49 (m, 2 H), 1.34–1.15 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164 (d, *J* = 249.6 Hz), 140.8, 128.7, 128.3, 126.3, 102.8 (d, *J* = 24.4 Hz), 37.4 (d, *J* = 26 Hz), 31.4 (d, *J* = 10.1 Hz), 29.6, 26.3, 25.9 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –114.6 (dd, *J* = 30.8, 22.2 Hz, 1 F, *E* isomer), –113.8 (dd, *J* = 38.0, 13.9 Hz, 1 F, *Z* isomer) ppm. IR (film) 2930, 2855, 1693, 1493, 1450, 1148, 1130, 735, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{19}FNa$ $[M+Na]^+$ 241.1368, found 241.1366.



1-benzyl-4-fluoro-1,2,3,6-tetrahydropyridine (2.6d)

The general procedure was followed using **2.5d** (117 mg, 0.250 mmol), *n*-BuLi (0.240 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (10% ether in hexanes) provided compound **2.6d** as a colorless liquid (11.0 mg, 23%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.28 (m, 5 H), 5.17 (dtt, *J* = 15.0, 7.1, 1.2 Hz, 1 H), 3.63 (s, 2 H), 3.04–3.01 (m, 2 H), 2.69 (td, *J* = 5.8, 2.1 Hz, 2 H), 2.34–2.31 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4 (d, *J* = 256 Hz), 138.4, 129.2, 128.5,

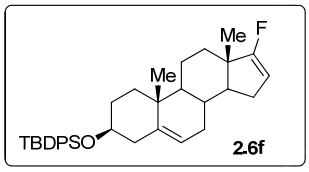
127.4, 100.5 (d, *J* = 14.6 Hz), 62.0 (d, *J* = 2.5 Hz), 50.3 (d, *J* = 9.1 Hz), 49.5 (d, *J* = 10.1 Hz), 26.7 (d, *J* = 22.4 Hz) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.3 (d, *J* = 15.4 Hz, 1 F) ppm. IR (film) 2928, 2802, 1713, 1454, 1375, 1119, 1028, 741, 700 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{15}FN$ $[M+H]^+$ 192.1189, found 192.1186.



2.6e

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

The general procedure was followed using **2.5e** (121 mg, 0.250 mmol), *n*-BuLi (0.230 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided compound **2.6e** as a colorless liquid (37.0 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.17 (m, 5 H), 4.60 (dd, *J* = 17.1, 2.5 Hz, 1 H), 4.52 (dd, *J* = 49.7, 2.5 Hz, 1 H), 4.02 (d, *J* = 13.1 Hz, 1 H), 3.25 (d, *J* = 13.1 Hz, 1 H), 3.07–2.99 (m, 1 H), 2.91 (t, *J* = 7.9 Hz, 1 H), 2.18 (q, *J* = 8.6 Hz, 1 H), 2.01–1.84 (m, 2 H), 1.80–1.66 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8 (d, *J* = 258.8 Hz), 139.4, 129.0, 128.4, 127.1, 91.1 (d, *J* = 18.8 Hz), 64.5 (d, *J* = 29.1 Hz), 58.3, 53.4, 29.3, 23.0 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.3 (dt, *J* = 49.6, 17.7 Hz, 1 F) ppm. IR (film) 2970, 2797, 1672, 1495, 1454, 1277, 1202, 910, 854, 739, 698 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{13}H_{16}FNNa$ $[M+Na]^+$ 228.1164, found 228.1158.



2.6f

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

The general procedure was followed using **2.5f** (121 mg, 0.150 mmol), *n*-BuLi (0.150 mL, 0.330 mmol), and NFSI (71 mg, 0.225 mmol). Workup and chromatographic purification (hexanes) provided compound **2.6f** as a colorless liquid (29.0 mg, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.67 (m, 4 H), 7.45 –7.35

(m, 6 H), 5.15 (d, *J* = 5.3 Hz, 1 H), 4.88–4.87 (m, 1 H), 3.58–3.50 (m, 1 H), 2.38–2.32 (m, 1 H), 2.18–2.13 (m, 1 H), 2.06–1.99 (m, 1 H), 1.97–1.80 (m, 2 H), 1.77–1.67 (m, 3 H), 1.65–1.57 (m, 2 H), 1.52–1.46 (m, 2 H), 1.41–1.34 (m, 1 H), 1.27 (br, 1 H), 1.07 (s, 9 H), 1.03 (s, 3 H), 0.97 (s, 3 H), 0.96–0.83 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0 (d, *J* = 287.1 Hz), 141.9, 136.0, 135.0, 129.7 (d, *J* = 2.3 Hz), 127.7 (d, *J* = 2.8 Hz), 120.8, 100.7 (d, *J* = 10.1 Hz), 73.4, 54.8 (d, *J* = 5.6 Hz), 50.9, 42.7, 42.5, 37.3, 36.9, 33.0, 32.1, 30.8, 30.1, 27.2, 27.1 (d, *J* = 7.0 Hz), 20.4, 19.5, 19.4, 15.3 (d, *J* = 4.0 Hz) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.9 (d, *J* = 4.5 Hz, 1 F) ppm. IR (film) 2932, 2856, 1651, 1462, 1427, 1371, 1109, 799, 739, 702, 613, 509 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{35}H_{45}FOSiNa$ $[M+Na]^+$ 551.3121, found 551.3145.

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

An oven-dried round flask (25 mL) was charged with ketone **2.7a**–**c** (0.50 mmol), TPSH (0.50 mmol) and a magnetic stir bar. The reaction vessel was equipped with a three-way valve, evacuated and backfilled with nitrogen. A pre-prepared stock solution of TFA (0.050 mmol) in THF (1.0 mL) was added and the reaction mixture was stirred at rt for 1.5 h. Then, the reaction solution was diluted with additional THF (1.5 mL) followed by the addition of activated 4Å molecular sieves (400 mg) and stirred at rt for 10 min. The solution was cooled to –78 °C, and then *n*-BuLi (1.5 mmol) was added dropwise into the pre-cooled and stirred solution at –78 °C. The resulting solution was stirred at –78 °C for 30 min to generate the dianion and at 0 °C for 20 min to release N_2. Subsequently, the reaction solution was cooled to –78 °C, and then a solution of NFSI (0.75 mmol, *c* = 0.50 M in THF) was added dropwise over 4 min. Additional THF (0.1 mL) was used to wash the vial, and added successively. The resulting solution was stirred at –78 °C for 30 min, and then at rt for 2 h. 0.50 N α,α,α-trifluorotoluene in EtOAc (200 μL, 0.10 mmol) was added as an internal standard and the resulting mixture was stirred at rt for 5 min. After standing for 3 min, an aliquot of the upper clear solution was removed and subjected to ^{19}F NMR analysis to determine yields of fluoroalkene **2.8a**–**c**.

References for Chapter 2 Experimental Section

[1] Kofron, W. G.; Baclawski, L. M. "A Convenient Method for Estimation of Alkyllithium Concentrations" *J. Org. Chem*. **1976**, *41*, 1879–1880.

[2] Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. "2,4,6-Tri-isopropylbenzenesulfonyl Hydrazide: A Convenient Source of Di-Imide" *Tetrahedron* **1976**, *32*, 2157–2162.

[3] Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. "Sila-Venlafaxine, A Sila-Analogue of the Serotonin/Noradrenaline Reuptake Inhibitor Venlafaxine: Synthesis, Crystal Structure Analysis, and Pharmacological Characterization" *Organometallics* **2006**, *25*, 1188–1198.

[4] Mislankar, D. G.; Mugrage, B.; Darling, S. D. "Enephosphinylation" *Tetrahedron Lett*. **1981**, *22*, 4619–4622.

[5] Dudman, C. C.; Reese, C. B. "Preparation of Aryldiazoalkanes from 2,4,6-Triisopropylbenzenesulfonyl Hydrazones" *Synthesis* **1982**, 419–421.

[6] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. "Vinyllithium Reagents from Arenesulfonylhydrazones" *J. Org. Chem*. **1978**, *43*, 147–154.

[7] Bertz, S. H.; Dabbagh, G. "Improved Preparations of Some Arenesulfonylhydrazones" *J. Org. Chem*. **1983**, *48*, 116–119.

[8] Miyazaki, T.; Maekawa, H.; Hisatomi, T.; Nishiguchi, I. "Highly Stereo- and Regio-selective Intramolecular Cyclization with Diastereoselective Asymmetric Induction by Electroreduction of Optically Active *N*-Alkenyl-2-acylpyrrolidines" *Electrochemistry* **2011**, *79*, 447–449.

[9] Calogeropoulou, T.; Avlonitis, N.; Minas, V.; Alexi, X.; Pantzou, A.; Charalampopoulos, I.; Zervou, M.; Vergou, V.; Katsanou, E. S.; Lazaridis, I.; Alexis, M. N.; Gravanis, A. "Novel Dehydroepiandrosterone Derivatives with Antiapoptotic, Neuroprotective Activity" *J. Med. Chem*. **2009**, *52*, 6569–6587.

[10] Hruschka, S.; Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Fröhlich, R.; Wibbeling, B.; Haufe, G. "Fluorinated Phenylcyclopropylamines. Part 5: Effects of Electron-Withdrawing or -Donating Aryl Substituents on the Inhibition of Monoamine Oxidases A and B by 2-Aryl-2-fluoro-cyclopropylamines" *Bioorg. Med. Chem*. **2008**, *16*, 7148–7166.

[11] Hanamoto, T.; Kobayashi, T. "Cross-Coupling Reactions of (1-Fluorovinyl)methyldiphenylsilane with Aryl Halides and Aryl Triflates" *J. Org. Chem*. **2003**, *68*, 6354–6359.

[12] Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. "β,β-Difluoro Analogs of α-Oxo-β-phenylpropionic Acid and Phenylalanine" *Tetrahedron* **2004**, *60*, 7731–7742.

[13] Sket, B.; Zupan, M. "Fluorination with Xenon Difluoride. Part 15. Stereochemistry of Fluorine Addition to Acenaphthylene and Dihydronaphthalenes" *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2169–2172.

[14] Wong, O. A.; Shi, Y. "Asymmetric Epoxidation of Fluoroolefins by Chiral Dioxirane. Fluorine Effect on Enantioselectivity" *J. Org. Chem*. **2009**, *74*, 8377–8380.

[15] Ghosh, A. K.; Zajc, B. "High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-Julia Olefinations" *Org. Lett*. **2006**, *8*, 1553–1556.

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

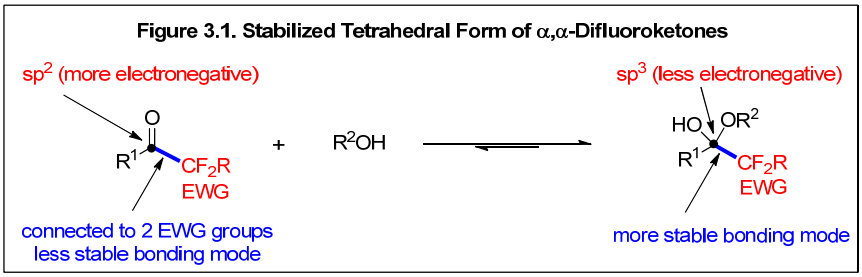
[17] Kirihara, M.; Takuwa, T.; Okumura, M.; Wakikawa, T.; Takahata, H.; Momose, T.; Takeuchi, Y.; Nemoto, H. "α-Bromo-α,α-difluoroallyl Derivatives as Synthetic Intermediates: Nucleophilic Substitution of α-Bromo-α,α-difluoroallyl Derivatives in the Presence of Palladium Catalysts" *Chem. Pharm. Bull*. **2000**, *48*, 885–888.

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

3.1 Introduction to α,α-Difluoroketones

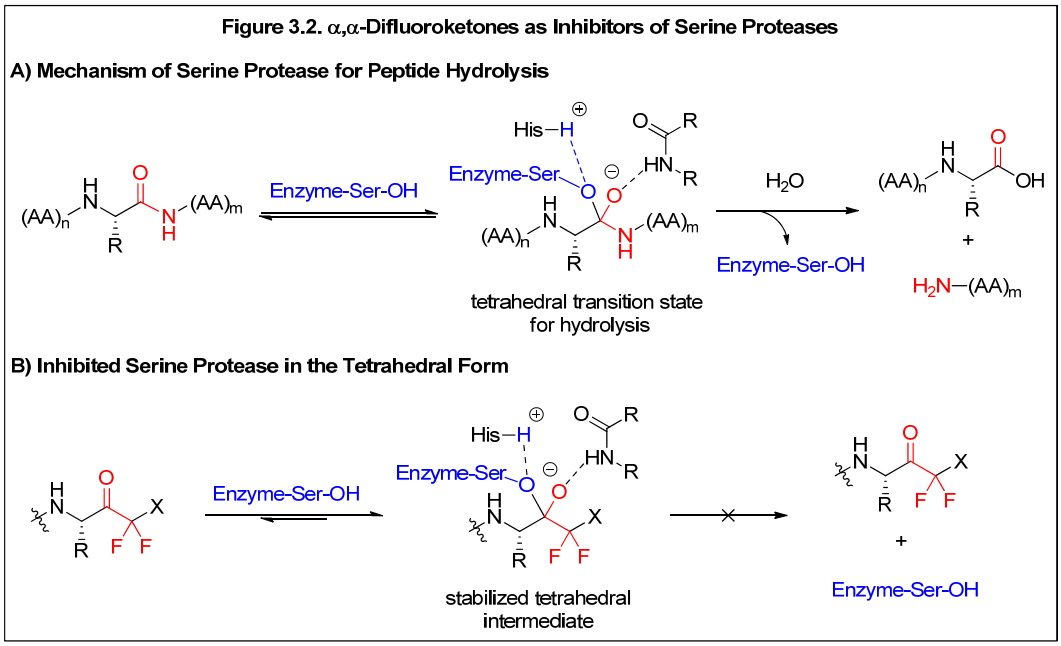
The α,α-difluoroketone represents a privileged substructure in medicinal chemistry, and serves as inhibitors to many hydrolytic enzymes, such as serine and aspartyl proteases.[1] For this substructure, the electron-withdrawing difluorinated group increases electrophilicity of the carbonyl group and encourages rehybridization of the sp^2-hybridized C=O to form sp^3-hybridized hydrates or hemi-hydrates (Figure 3.1).[2] In the hydrates, sp^3-hybridized carbon forms more stable bonding with electron-deficient fluorinated groups based on Bent's rule, which requires that an atom uses more p-character in forming a bond with an electronegative substituent. Thus, the equilibrium constant shifts toward the direction of hydrates. The stabilized tetrahedral hydrate intermediates mimic the transition state of hydrolytic processes catalyzed by proteases and inhibit enzymes from acting on their peptide substrates. This tendency of favorable rehybridization to generate stabilized tetrahedral intermediates enables α,α-difluoroketones an important motif in the design of protease inhibitors.

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



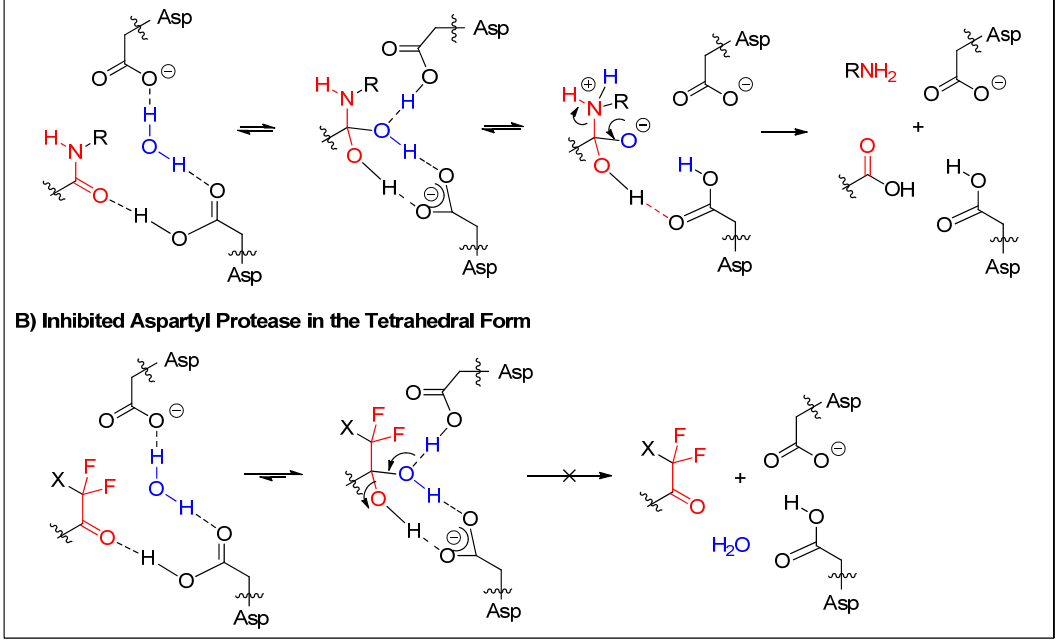
In serine proteases, the hydroxyl group of serine amino acids attacks the carbonyl group of an amide bond on the substrates to form a tetrahedral intermediate, and then the collapse of the intermediate cleaves an amide bond and regenerates the enzymes (Figure 3.2A). Similarly, α,α-difluoroketone-bearing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

Figure 3.2. α,α-Difluoroketones as Inhibitors of Serine Proteases



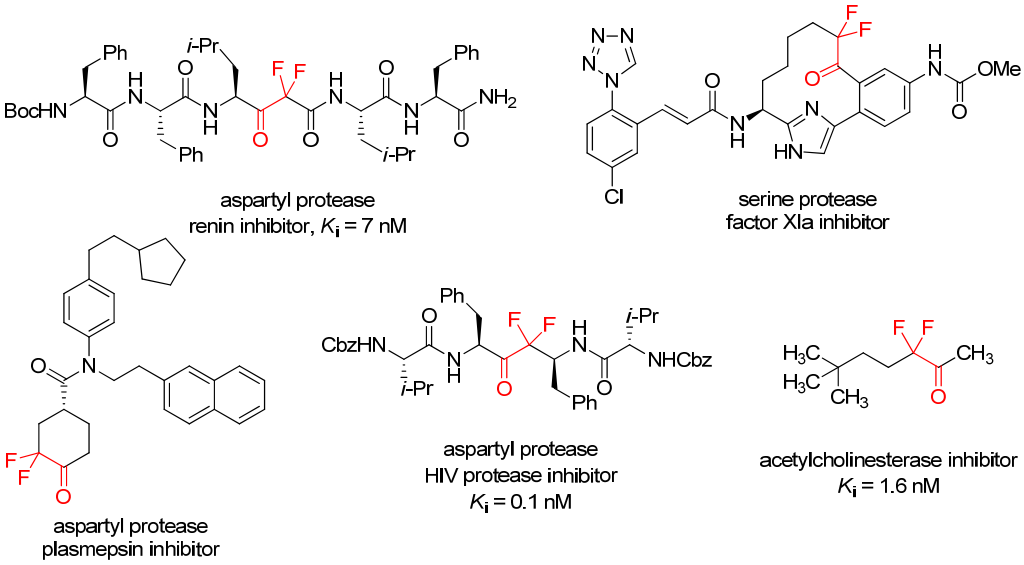
In aspartyl proteases, a water molecule activated by two aspartyl residues in the active site of the enzymes attacks carbonyl group of an amide bond on the substrates to form a tetrahedral intermediate, and then the collapse of the intermediate cleaves an amide bond and releases the water molecule (Figure 3.3A). For α,α-difluoroketone inhibitors, the activated water molecule reacts with the carbonyl group of α,α-difluoroketones to form a long-lasting stabilized adduct, which occupies in the active site of aspartyl proteases and prevents the peptide substrates from entering the hydrolytic site. Herein, α,α-difluoroketones react with a water molecule and inhibit aspartyl proteases *via* non-covalent H-bonding networks (Figure 3.3B).[1,3a]

Figure 3.3. α,α-Difluoroketones as Inhibitors of Aspartyl Proteases



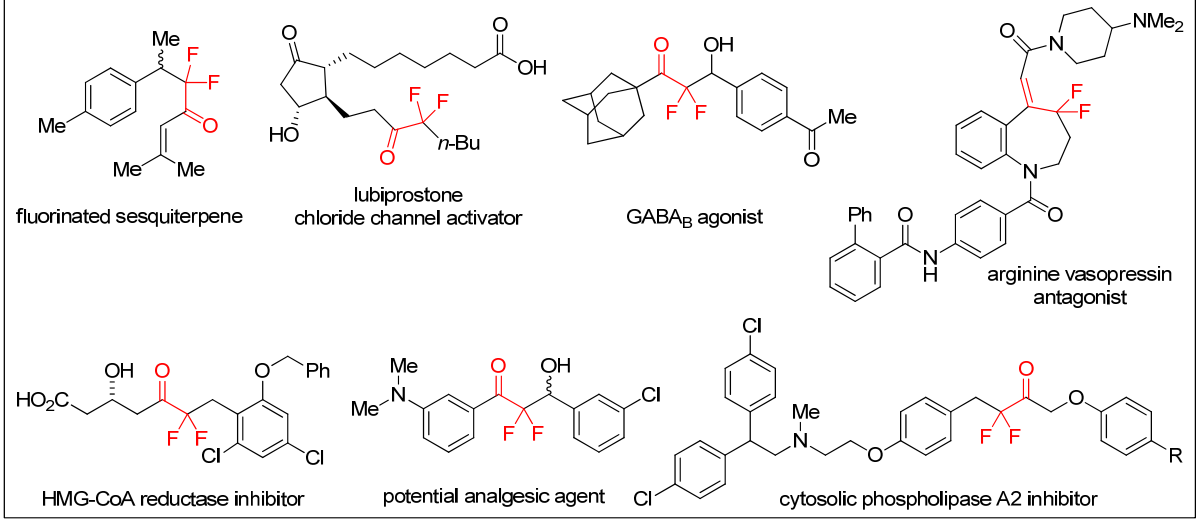
Based on these mechanisms, α,α-difluoroketones serve as inhibitors of hydrolytic enzymes, some of which exhibit subnanomolar K_i constants, including inhibitors of HIV proteases, human renin, and acetylcholinesterases (Figure 3.4).[3,4]

Figure 3.4. Representative Examples of α,α-Difluoroketones as Inhibitors of Hydrolytic Enzymes



Furthermore, this substructure can be introduced into natural products,[5a] and in inhibitors of non-protease targets that provide distinct pharmacological profiles (Figure 3.5).[5b–f] Additionally, this substructure can serve as an intermediate for further functionalization; for example, olefination reaction to generate α,α-difluoroalkenes in the structure of arginine vasopressin antagonists (Figure 3.5).[5g]

Figure 3.5. Representative Examples of Bioactive Molecules Bearing α,α-Difluoroketone Motifs



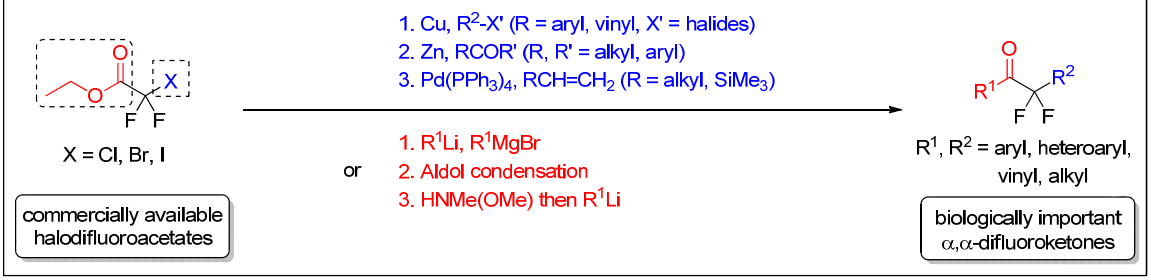
3.2 Literature Review to Access α,α-Difluoroketones

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

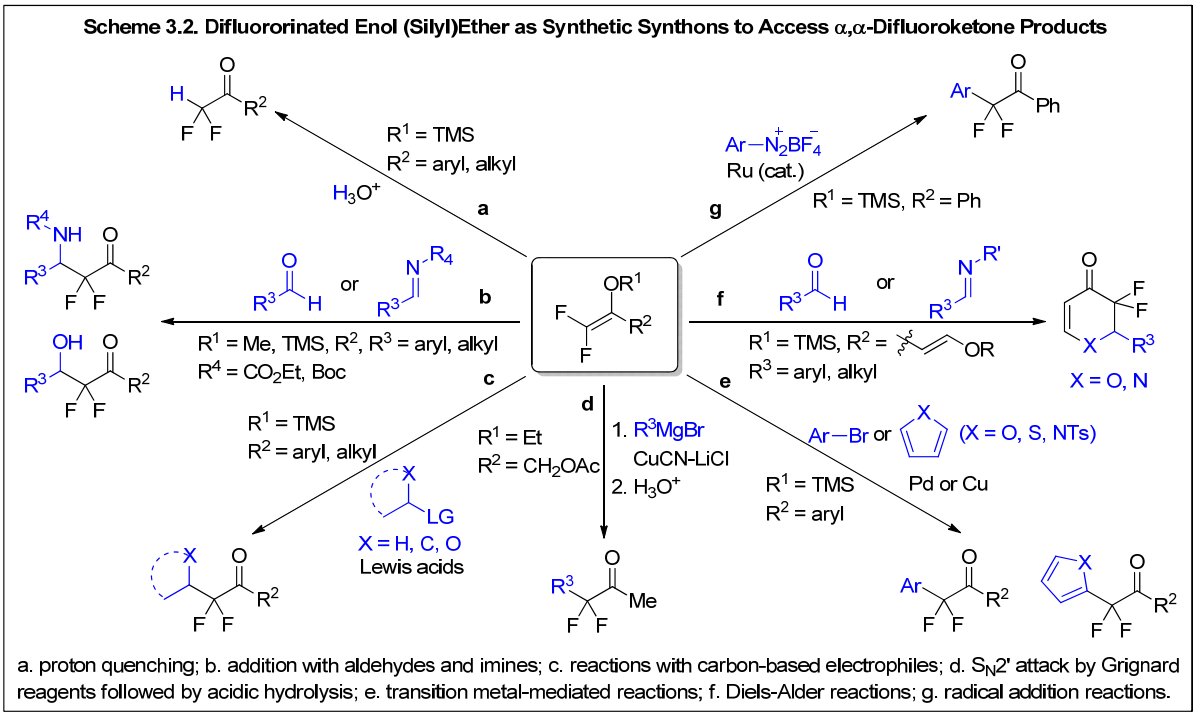
3.2.1 Building Block Strategy

The building block strategy is a common method to access α,α-difluoroketone derivatives in medicinal chemistry. This method uses commercially available halodifluoroacetates as difluoromethyl synthons to access the final α,α-difluoroketone targets *via* multistep synthetic transformations (Scheme 3.1).[5f,6] However, these conversions of functional groups cause a time- and labor-consuming process, which is a major disadvantage of this method.

Scheme 3.1. Building Block Strategy to Access α,α-Difluoro-Functionalized Ketones

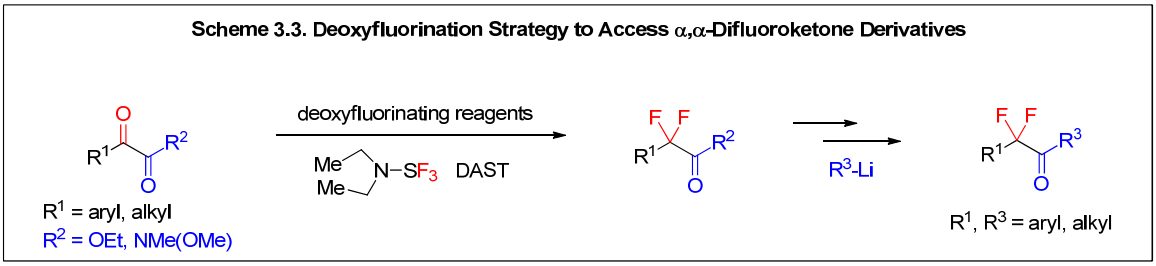


Difluoroenoxysilanes and difluorinated enol ethers are important reactants that enable access to α,α-difluoroketone derivatives through a variety of reactions (Scheme 3.2). For example, difluoroenoxysilanes serve as nucleophiles and react with protons (path a, Scheme 3.2),[7a] carbonyl groups (path b, Scheme 3.2),[7b] imines (path b, Scheme 3.2),[7c,d] and carbon-based electrophiles in the presence of Lewis acids (path c, Scheme 3.2),[7e,f] to provide α,α-difluoroketone derivatives. On the other hand, difluorinated enol ethers act as electrophiles and undergo S_N2' attack by Grignard reagents to generate enol ethers, which afford the α,α-difluoroketone products after acidic hydrolysis (path d, Scheme 3.2).[7g] Additionally, difluoroenoxysilanes are used as coupling components in transition metal-mediated coupling reactions (path e, Scheme 3.2), in which difluoroenoxysilanes act as nucleophiles to react with electrophiles,[7h] or to couple with nucleophiles in the presence of oxidants[7i] to form α-substituted α,α-difluoroketones. Moreover, difluoroenoxysilanes serve as fluorinated Danishefsky's dienes in hetero Diels-Alder reactions and react with aldehydes and imines to generate *N*- and *O*-containing six-membered α,α-difluoroketones (path f, Scheme 3.2).[7j] A recent report demonstrates the participation of difluoroenoxysilanes in radical addition reactions (path g, Scheme 3.2).[7k] In the reactions, difluoroenoxysilanes play a role of electron sink and receive a aryl radical generated from arene diazonium salts *via* a photo-initiated nitrogen-releasing process. Subsequent oxidation of the resulting radicals followed by removal of a TMS group produce α-arylated α,α-difluoroketones. Conclusively, these versatile synthetic transformations, based on difluorinated enol (silyl) ethers, provide a variety of α,α-difluoroketone-bearing molecules.



3.2.2 Deoxyfluorination Strategy

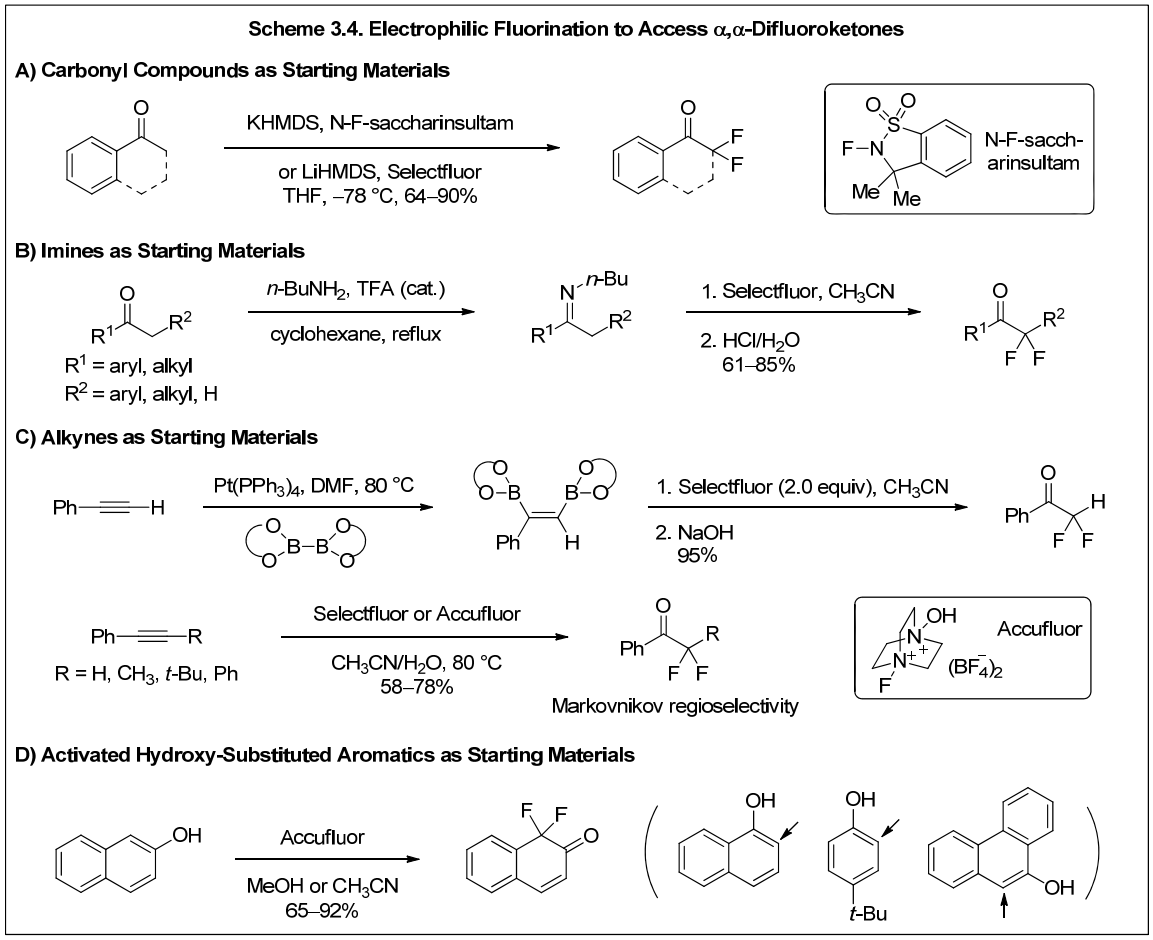
This method utilizes deoxyfluorinating reagents to convert the carbonyl group C=O of 2-oxoacetic acid derivatives to the difluoromethylene CF_2 group. Subsequent addition of organolithium or Grignard reagents to the resulting α,α-difluoracetic acid derivatives provides α,α-difluoroketone products (Scheme 3.3).[5d–e,8] However, the reactions require the use of strong deoxyfluorinating reagents, which are not compatible with many important functional groups and suffer from side reactions, such as eliminations, thus leading to limited substrate scope.



3.2.3 Electrophilic Fluorination Strategy

Electrophilic fluorination has been developed for synthesizing α,α-difluoroketones from carbonyl compounds,[9a,b] imines,[9c] alkynes[9d–f] and activated aromatics[9f,g] using Selectfluor®, *N*-fluorosulfonimides,

CF_3OF and $FOSO_2OCs$ as fluorinating reagents (Scheme 3.4). However, most of the reactions require the use of strong bases to facilitate difluorination of less reactive mono-carbonyl substrates (Scheme 3.4A), which are not suitable for base-sensitive and highly functionalized molecules. Although the use of imines and benzophenol derivatives provides α,α-difluoroketones under mild conditions, extra synthetic steps are required to acquire these pre-functionalized precursors (Scheme 3.4B and 3.4D). These drawbacks detract its wide application in the late stage fluorination to access α,α-difluoroketones.

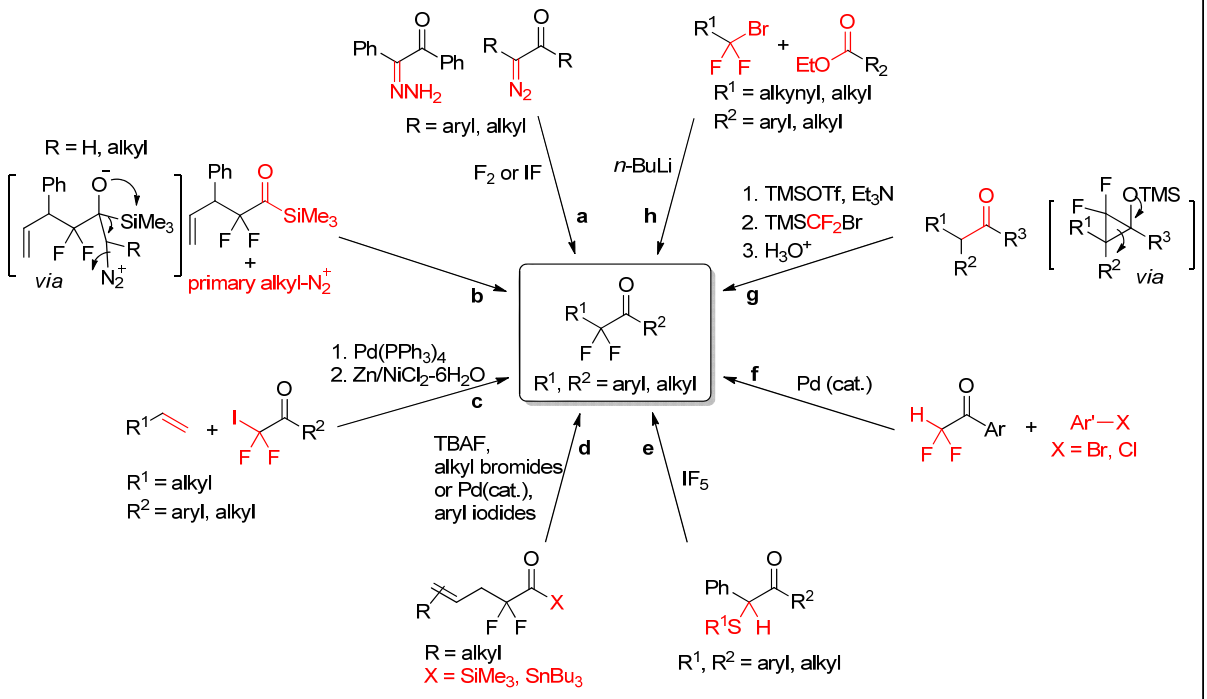


3.2.4 Miscellaneous Strategies

Other methods, including nucleophilic fluorination of α-diazo- and α-hydrazone ketones (path a, Scheme 3.5),[10a,b] Brook rearrangement of the α,α-difluoroacylsilanes with primary diazoalkanes (path b, Scheme 3.5),[10c] radical addition of halodifluoroketone to alkenes (path c, Scheme 3.5),[10d] and Claisen rearrangement of the vinylsilanes or -stannanes followed by fluoride-mediated alkylation or Stille

coupling (path d, Scheme 3.5)[10e] provided a variety of α,α-difluoroketone products. Recently, different types of reactions have been created for accessing α-aryl and α-alkyl substituted α,α-difluoroketones, such as desulfurization-fluorination (path e, Scheme 3.5),[10f] transition metal-catalyzed coupling reactions of the difluoromethyl ketones with aryl halides (path f, Scheme 3.5),[10g,h] difluorohomologation of ketones (path g, Scheme 3.5),[10i] and addition of difluoroalkyl anions to esters (path h, Scheme 3.5).[10j] However, most of these reactions are illustrated by the limited examples, characterized by a narrow range of substrates, thus they are not extensively applied in preparing α,α-difluoroketone derivatives.

Scheme 3.5. Alternative Methods to Access α,α-Difluoroketone Products



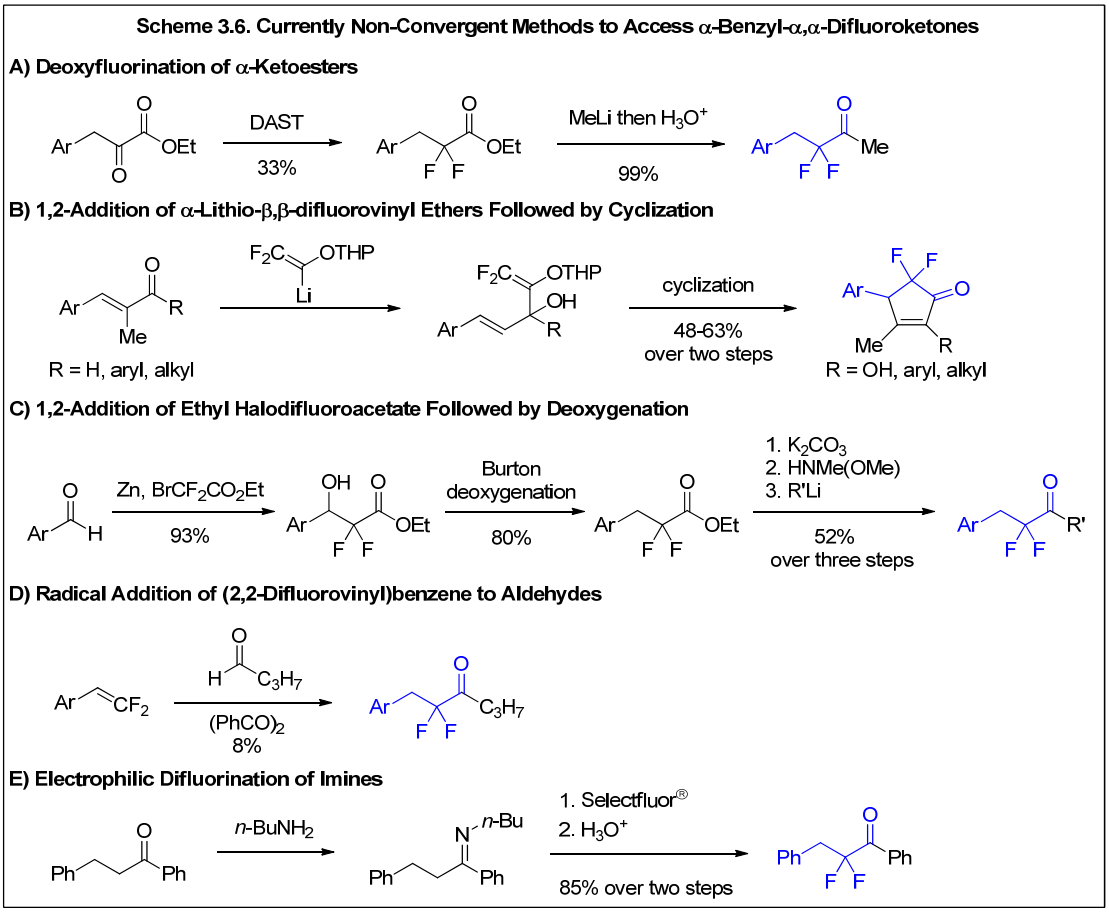
a. nucleophilic fluorization of α-diazo- and α-hydrazone ketones; b. Brook rearrangement of α,α-difluoroacylsilanes with primary diazoalkanes; c. radical addition of halo-difluoroketones to alkenes; d. fluoride-mediated alkylation or Stille coupling; e. desulfurization -fluorization; f. transition metal-catalyzed coupling reactions of difluoromethyl ketones with aryl halides; g.difluorohomologation of ketones *via* ring opening of cyclopropanes; h. addition of difluoroalkyl anions to esters.

3.2.5 Strategies to Access α-Benzyl-α,α-difluoroketones

Despite the many methods described above that have been reported in synthesizing α,α-difluoroketones, most of them rely on multiple transformations to access the final targets, which are not convergent strategies. Furthermore, efficient methods to generate α-alkyl-α,α-difluoroketones are less explored. Several alternative strategies for accessing α-benzyl-α,α-difluoroketones have been developed,

including: 1) deoxyfluorination of α-ketoesters using strong fluorinating reagents, followed by addition of organolithium or Grignard reagents to the resulting α,α-difluoroester (Scheme 3.6A), for which the strong bases and harsh reagents destroy many functional groups;[5d] 2) 1,2-addition of α-lithio-α,α-difluorovinyl ethers to aldehydes/ketones followed by cyclization of the resulting alcohol (Scheme 3.6B), which only accesses a small subset of products;[11a] 3) 1,2-addition of ethyl halodifluoroacetate to aldehydes followed by deoxygenation (Scheme 3.6C);[5f] 4) a single radical addition reaction of an aldehyde to a (2,2-difluorovinyl)benzene (Scheme 3.6D);[11b] and 5) a late-stage electrophilic difluorination of prefunctionalized imines using Selectfluor/NFSI followed by acid-mediated hydrolysis (Scheme 3.6E)- not a convergent strategy,[9c] which also generates a mixture of fluorinated products for substrates bearing two sites capable of undergoing imine-enamine isomerization. However, none of these reactions convergently generate the α-benzyl-α,α-difluoroketones.

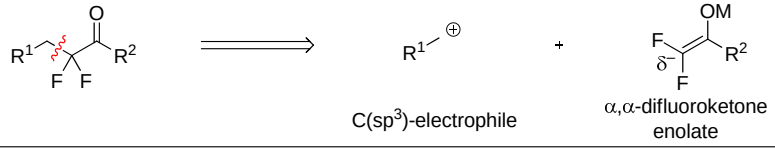
Scheme 3.6. Currently Non-Convergent Methods to Access α-Benzyl-α,α-Difluoroketones



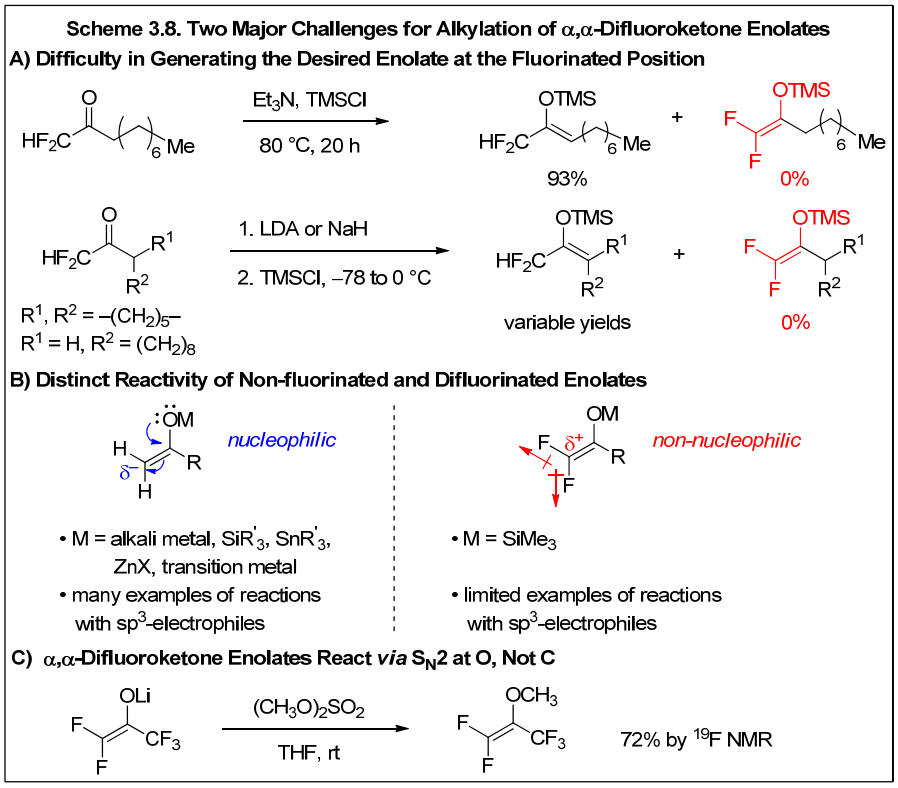
3.3 Challenges to Access α-Alkyl-α,α-Difluoroketones

A convergent preparation of α-alkyl-α,α-difluoroketones would involve a transformation capable of generating a C(α)–C(sp^3) bond, presumably by reacting a nucleophilic α,α-difluoroketone enolate with an sp^3-hybridized electrophile (Scheme 3.7).

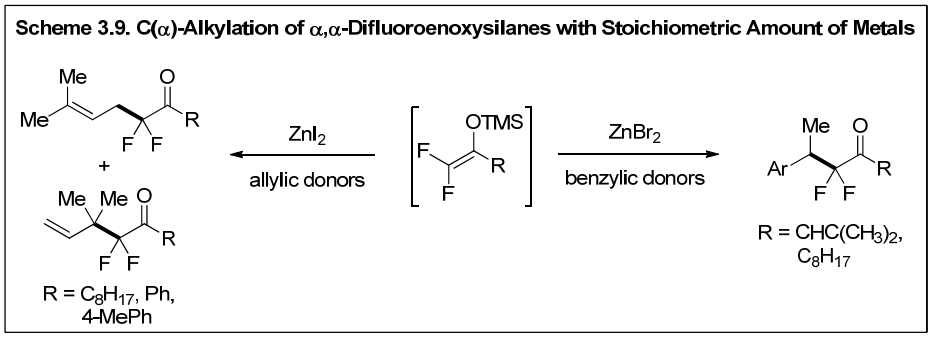
Scheme 3.7. Desired Retrosynthetic Disconnection of the Critical C(α)–C(sp^3) Bond



Alkylation of ketone enolates with sp^3-based electrophiles is a fundamental transformation for accessing a broad spectrum of α-functionalized ketones.[12] However, nucleophilic substitution reactions of α,α-difluorinated ketone enolates with sp^3-based electrophiles have not been generally developed, because of two problems. First, chemoselective formation of α,α-difluoroketone enolates presents challenges, because deprotonation of α,α-difluoromethyl ketones produces enolates at the nonfluorinated position under both thermodynamic and kinetic conditions (Scheme 3.8A),[13] and upon trapping, cannot afford α-functionalized-α,α-difluoroketones. Second, α,α-difluoroketone enolates possess unique physicochemical properties that preclude formation of the C(α)–C(sp^3) bond. Specifically, the strong inductive effect of the two fluorine atoms[14a] decreases the charge density of an enolate at the α-position,[14b] and thus reduces the nucleophilicity of the anion and disfavors reactions with sp^3-based electrophiles (Scheme 3.8B). As a result, α,α-difluoroketone enolates react by S_N2 reactions at the O to generate difluorovinyl ethers, instead of at C(α) (Scheme 3.8C).[15]



Because of these two factors, only two manuscripts describe S_N1- or S_N2-like alkylation reactions of α,α-difluoroketones, and both require stoichiometric amount of metal reagents to promote the reactions (Scheme 3.9).[16]

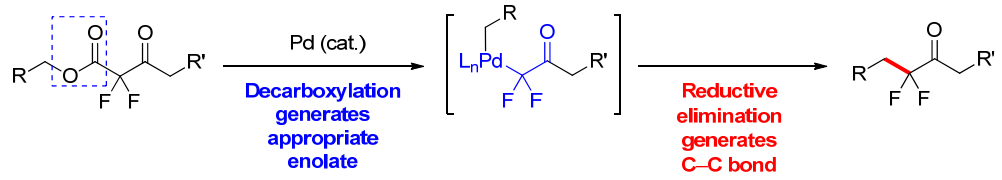


3.4 Palladium-Catalyzed Decarboxylative Difluoroalkylation to Access α-Benzyl-α,α-difluoroketones

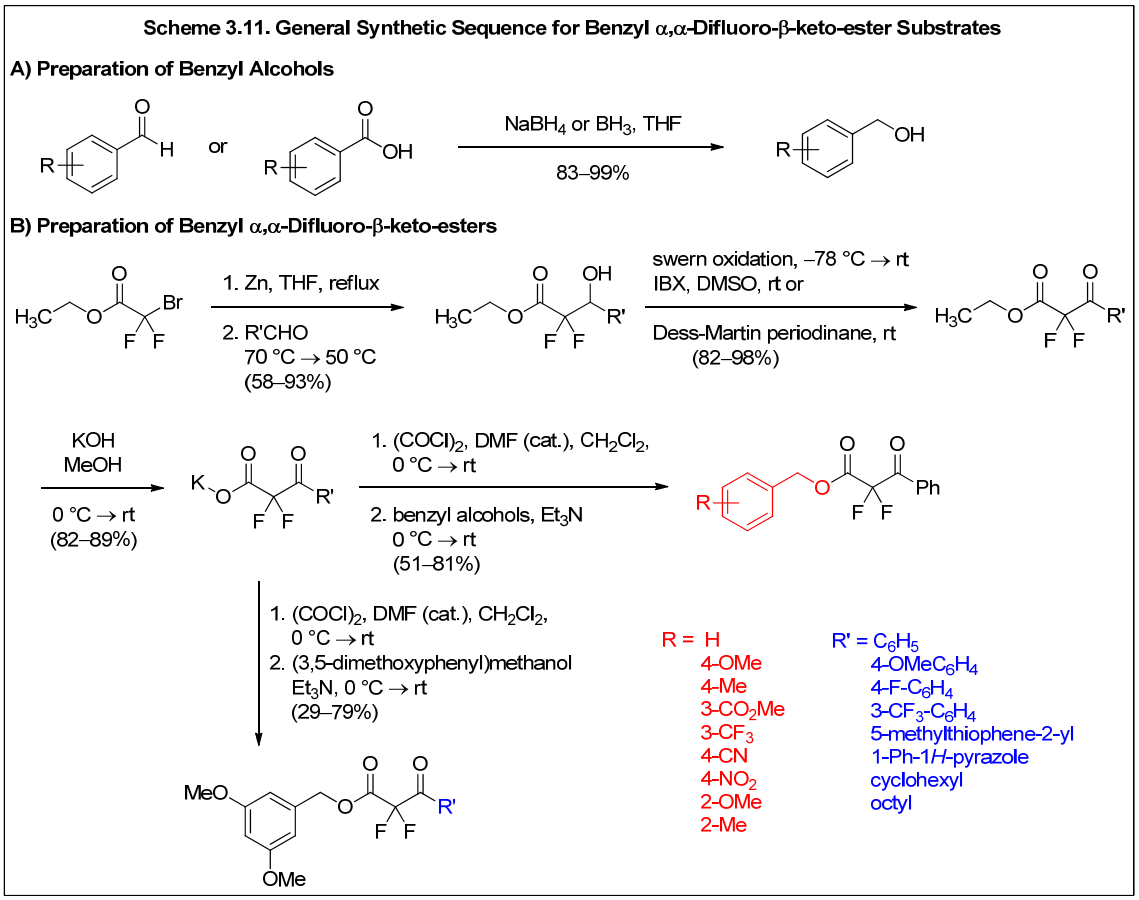
Because of the previously discussed challenges with forming α,α-difluoroketone enolates by conventional base deprotonation and alkylation, an alternative strategy is necessary for accessing the reactive enolates. It has been reported that non-fluorinated ketone enolates can be generated *in situ via* a decarboxylative coupling process, which enables the regioselective formation of reactive enolate

nucleophiles that might be difficult to access otherwise,[17] followed by a C–C bond-forming event. Thus, we predicted that a decarboxylative protocol could generate α,α-difluoroketone enolates. Moreover, we assumed the low reactivity of α,α-difluoroketone enolates could be overcome by a transition metal mediator that can link the nucleophilic enolate with the electrophile and facilitate the reaction. Combining these thoughts, a Pd-catalyzed decarboxylative strategy was explored to address two major challenges associated with alkylation reactions of α,α-difluoroketone enolates, and to generate α-alkyl-α,α-difluoroketones (Scheme 3.10). Although recently reported reactions have coupled α,α-difluoroketone enolates with aryl halides,[7h,10g,h] rarely has a Pd-based catalytic system effectively promoted the alkylation reaction of α,α-difluoroketone enolates. In this proposed reaction, a decarboxylative strategy would chemoselectively generate the appropriate α,α-difluoroketone enolate, and the critical C(α)–C(sp^3) bond would form by reductive elimination from a high-energy [L_nPd(benzyl)(α,α-difluoroenolate)] intermediate (Scheme 3.10).

Scheme 3.10. Proposed Decarboxylative Strategy to Access α-Alkyl-α,α-difluoroketones

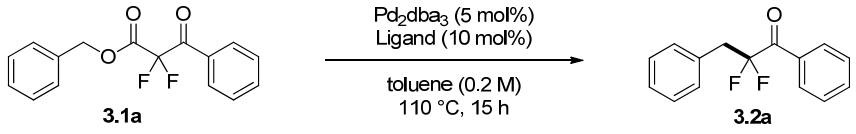


To begin the study, benzylic electrophiles were selected because they possess higher reactivity compared to alkyl electrophiles, and the α,α-difluoroketone enolates would be generated *in situ via* decarboxylation of α,α-difluoro-β-keto-esters. Thus, benzyl α,α-difluoro-β-keto-esters were identified as test substrates, and they were prepared through four steps, comprising 1) Reformatsky addition of ethyl bromodifluoroacetate to aldehydes; 2) oxidation of alcohols to ketones; 3) basic hydrolysis of ethyl esters; and 4) esterification of β-keto-α,α-difluoroacetate with benzyl alcohols (Scheme 3.11).



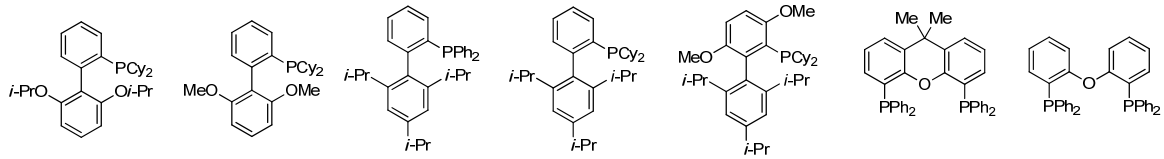
Initial screening was performed by Niusha Sharifi,[18] who focused on the identification of appropriate ligands that form metal catalysts to activate the substrate, stabilize the [L_nPd(benzyl)(α,α-difluoroenolate)] intermediate, and facilitate the C–C bond formation. Our screening identified certain biarylmonophosphine-based ligands derived from RuPhos, SPhos, PhXPhos, XPhos and BrettPhos scaffolds,[19] and bidentate phosphine ligands such as Xantphos and DPEPhos that could generate the coupled product **3.2a** in modest yields (Scheme 3.12A). Other ligands failed to produce at least 15% of the coupled product **3.2a** (Scheme 3.12B).

Scheme 3.12. Preliminary Ligand Screening of Pd_2dba_3-Catalyzed Decarboxylative Difluorobenzylation[a,b,c]



3.1a → 3.2a

A) Ligands that Provided Modest Yields

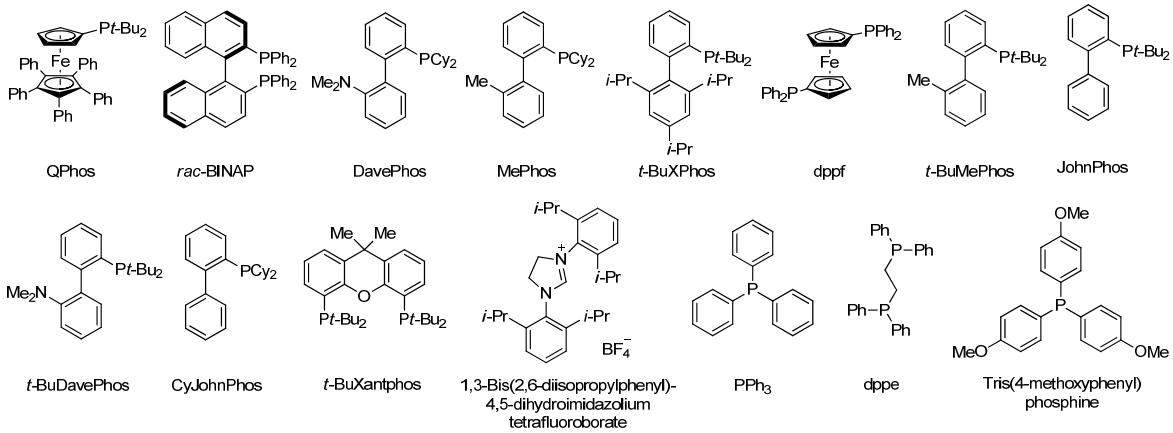


66% RuPhos | 69% SPhos | 66% PhXPhos | 53% XPhos | 48% BrettPhos | 44% Xantphos | 50% DPEPhos

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

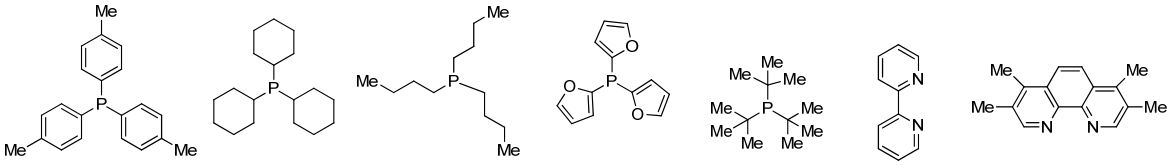
[b] The conversion for all reactions above was more than 99%, and protonated α,α-difluoroketone was the major side product.

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



QPhos | *rac*-BINAP | DavePhos | MePhos | *t*-BuXPhos | dppf | *t*-BuMePhos | JohnPhos

t-BuDavePhos | CyJohnPhos | *t*-BuXantphos | 1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate | PPh_3 | dppe | Tris(4-methoxyphenyl) phosphine

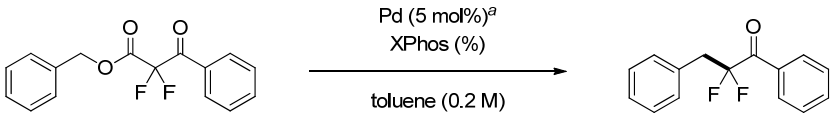


Tri(*p*-tolyl)phosphine | PCy_3 | P*n*-Bu_3 | Tri(2-furyl)phosphine | P*t*-Bu_3 | 2,2'-Bipyridine | 3,4,7,8-Tetramethyl-1,10-phenanthroline

[c] We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation disclosed above.

Subsequent thorough and systematic screening of palladium-based catalysts and precatalysts identified $Pd(PPh_3)_4$ as an efficient catalyst for the present transformation that afforded comparable yields as other systems containing Pd/ligands (entry 8, Table 3.1). After further optimization of solvent, temperature, Pd loading, and concentration, the final conditions [2.5% $[Pd(PPh_3)_4]$/*o*-xylene/120 °C] readily generated the desired α-benzyl-α,α-difluoroketone (entry 15, Table 3.2), thus confirming our hypothesis that transition metal catalysis should form the critical C(α)–C(sp^3) bond.

Table 3.1. Preliminary Screening of Pd Sources for Pd-Catalyzed Decarboxylative Difluorobenzylation

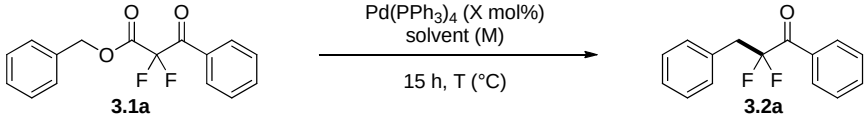


3.1a **3.2a**

entry	Pd	XPhos (%)	yield (%)[b]	conv. (%)
1	Pd_2dba_3	10	43	100
2	$PdCl_2$	15	7	56
3	$Pd(OAc)_2$	15	43	100
4	$Pd(TFA)_2$	15	21	95
5	$Pd(CH_3CN)_2Cl_2$	15	23	78
6	$Pd(acac)_2$	15	0	35
7	$Pd(\eta^3\text{-}C_2H_5)_2Cl_2$	15	37	100
8	$Pd(PPh_3)_4$	0	45	100

[a] Pd (5 mol%) indicates dimeric Pd (2.5 mol%) and monomeric Pd (5 mol%).
[b] Yields were determined by GC using dodecane as an internal standard.
[c] We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation.

Table 3.2. Optimization of $Pd(PPh_3)_4$-Catalyzed Decarboxylative Difluorobenzylation



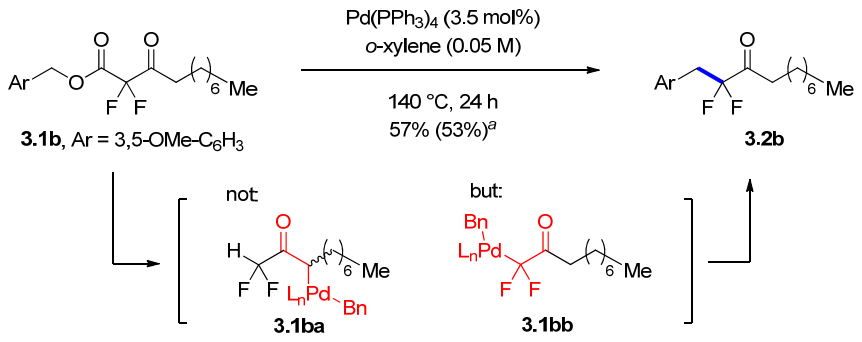
3.1a **3.2a**

entry	Pd (%)	solvent	conc. (M)	T (°C)	yield (%)[a]	conv. (%)
1	5	toluene	0.2	110	45	100
2	5	DME	0.2	100	4	100
3	5	2-Me-THF	0.2	80	10	98
4	5	DMF	0.2	80	1	94
5	5	1,4-dioxane	0.2	100	41	100
6	5	CH_3CN	0.2	80	0	69
7	5	*o*-xylene	0.2	120	78	100
8	5	*o*-xylene	0.2	130	76	100
9	2.5	*o*-xylene	0.2	120	(74)	100
10	1.0	*o*-xylene	0.2	120	58	100
11	2.5	*o*-xylene	1.0	120	(55)	100
12	2.5	*o*-xylene	0.5	120	(66)	100
13	2.5	*o*-xylene	0.3	120	(70)	100
14	2.5	*o*-xylene	0.1	120	(75)	100
15	2.5	*o*-xylene	0.05	120	(87)	100

[a] Yields were determined by GC using dodecane as an internal standard. The value in parentheses was ^{19}F NMR yields using α,α,α-trifluorotoluene as an internal standard.
[b] We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation.

As previously noted, alkylation reactions of α,α-difluoroketone enolates suffer from two classical problems, namely, generation of the appropriate enolate[13] and alkylation at C(α) instead of at O.[15] Although the example **3.2a** (Table 3.2) confirms the ability of the palladium-catalyzed system to generate the C(α)–C(sp^3) bond, the substrate **3.1a** does not bear enolizable H-atoms at the nonfluorinated α-position of the ketone, and therefore cannot form a nonfluorinated enolate. As such, **3.1a** does not confirm whether the Pd-catalyzed decarboxylative protocol would selectively generate the fluorinated ketone enolate. To address this concern, the reaction of aliphatic substrate **3.1b**, which could theoretically decarboxylate and isomerize to generate the undesired enolate **3.1ba** at nonfluorinated position (Scheme 3.13), was explored. Subjection of **3.1b** to [$Pd(PPh_3)_4$] at 140 °C, generated product **3.2b** in 53% isolated yield, with no detectable products arising from alkylation at the nonfluorinated position (Scheme 3.13). Thus, the present decarboxylative reaction overcomes both previously presented challenges associated with alkylation reactions of α,α-difluoroketone enolates.

Scheme 3.13. Decarboxylative Strategy Chemoselectively Generated the Desired Enolate and Enabled the Formation of the Key C(α)–C(sp^3) Bond

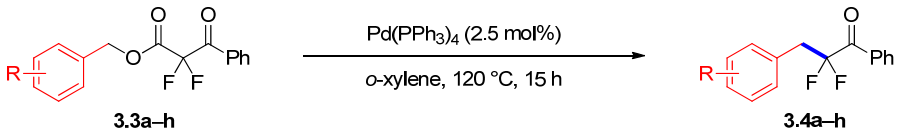


[a] ^{19}F NMR Yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs).

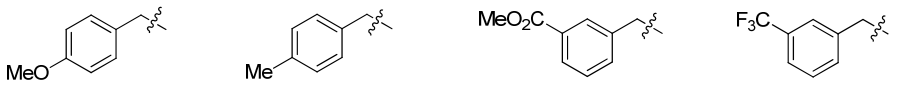
A variety of substrates bearing electron-rich, -neutral, and -deficient benzylic moieties underwent the decarboxylative reaction to generate α-benzyl-α,α-difluoroketones (Scheme 3.14). Generally, the optimized conditions converted electron-rich, and -neutral substrates into products **3.4a**–**b** and **3.2a** in high yields. However, moderately electron-deficient substrates required higher catalyst loading and/or reaction temperatures to provide good yields of products **3.4c**–**d**. Further, substrates bearing strong

electron-withdrawing groups were less active, and generated products **3.4e–f** in lower yields, even after optimization. This trend implicates the intermediacy of [Pd-(π-benzyl)(α,α-difluoroenolate)], as electron-donating groups stabilize the intermediate and facilitate the reaction, and electron-withdrawing groups destabilize the intermediate and retard the reaction (Scheme 3.15).[20] While the electronic nature of substrates affected the outcome of the reaction, steric effects did not impede the reaction. Reactions of *ortho*-substituted benzyl esters afforded products in comparably high yields to the analogous *para*-substituted substrates (**3.4g–h** versus **3.4a–b**).

Scheme 3.14. Decarboxylative Difluorobenzylation of Substrates Bearing Distinct Benzyl Moieties[a]



3.3a–h **3.4a–h**

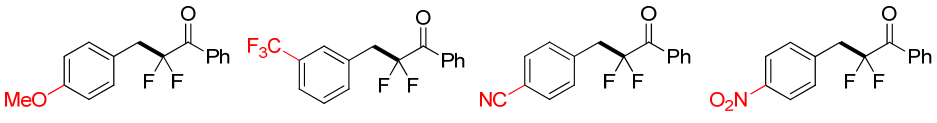


3.4a, 94% (83%) **3.4b**, 95% (85%) **3.4c**, 88% (80%)[b] **3.4d**, 66% (60%)[c]

3.4e, 35% (31%)[d] **3.4f**, 28% (22%)[e] **3.4g**, 95% (89%) **3.4h**, 97% (87%)

[a] Standard reaction conditions: **3.3a–h** (1.0 equiv), $Pd(PPh_3)_4$ (2.5 mol%), *o*-xylene (0.05 M), 120 °C, 15 h. ^{19}F NMR Yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs). [b] $Pd(PPh_3)_4$ (5.0 mol%). [c] $Pd(PPh_3)_4$ (5.0 mol%), 140 °C. [d] $Pd(PPh_3)_4$ (20 mol%), 140 °C, *o*-xylene (0.01 M), 24 h. [e] $Pd(PPh_3)_4$ (5.0 mol%), 140 °C, 24 h.

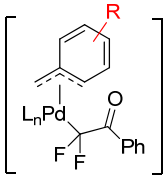
Scheme 3.15. Pd-π-Benzyl Complex Was Involved in the Reactions



$\sigma_p = -0.27$ $\sigma_m = 0.43$ $\sigma_p = 0.66$ $\sigma_p = 0.78$

83% 60% 31% 22%

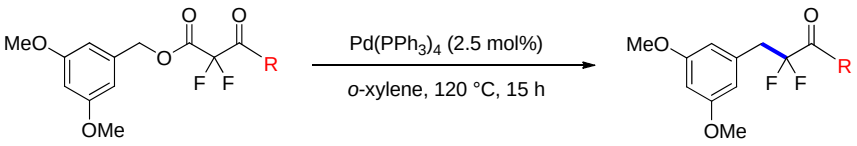
Stabilized Pd-π-Benzyl Complex Benefited Reactions



Destabilized Pd-π-Benzyl Complex Slowed Reactions

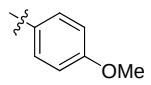
The decarboxylative reaction also successfully produced products bearing a variety of aryl- and alkyl α,α-difluoroketone moieties (Scheme 3.16). Reactions of substrates bearing electron-rich, -neutral and -withdrawing aryl α,α-difluoroketones provided the corresponding products **3.6a**–**c** in high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

Scheme 3.16. Decarboxylative Difluorobenzylation of Substrates Bearing Distinct Ketone Moieties[a]

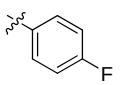


3.5a–f **3.6a–f**

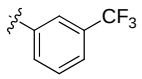
R =



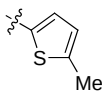
3.6a, 89% (75%)



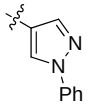
3.6b, 93% (80%)



3.6c, 85% (75%)[b]



3.6d, 92% (83%)



3.6e, 76% (66%)[c]

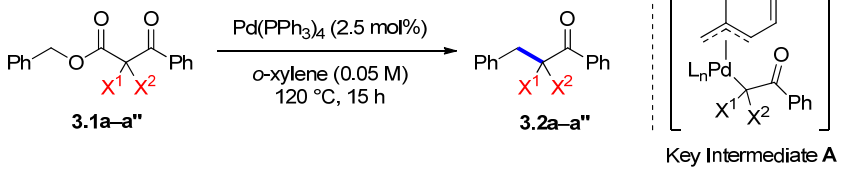
3.6f 61% (57%)[b]

[a] Standard reaction conditions: **3.5a**–**f** (1.0 equiv), $Pd(PPh_3)_4$ (2.5 mol%), *o*-xylene (0.05 M), 120 °C, 15 h. ^{19}F NMR Yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs). [b] 130 °C, 24 h. [c] 24 h.

This catalyst system only coupled the α,α-difluorinated substrate (entry 1, Table 3.3), while the mono- and nonfluorinated substrates did not provide the expected products (entries 2–3, Table 3.3). This dramatic fluorine effect facilitated the present reaction with neutral and even electron-deficient benzyl esters, while some other transformations involving oxidative addition of $Pd(PPh_3)_4$ into nonfluorinated benzyl esters typically require an extended conjugated system or an electron-rich benzylic moiety.[21] This phenomenon likely reflects the strong σ-withdrawing inductive effect of the two fluorine atoms, which increases the electrophilicity of the substrate, and accelerates the oxidative addition step to generate the high-energy dearomatized π-benzyl intermediate (**A**,[22] Table 3.3).[17a,23] In contrast, we believe that the

fluorine substituents likely do not accelerate the decarboxylation step of the reaction. Despite the increased stability of the α,α-difluorinated enolate (ketone-CF_2H pK_a = 20.2; ketone-CFH_2 pK_a = 21.7; ketone-CH_3 pK_a = 24.7),[24] rehybridization of α,α-difluorinated enolate carbanions from C(sp^3) to C(sp^2) actually occurs more slowly than nonfluorinated enolates,[25] which contradicts the trend observed (Table 3.3).

Table 3.3. Fluorine Atoms Increased Reactivity of Substrate toward Pd-Catalyzed Decarboxylative Benzylation of α,α-Difluoroketone Enolates.[a]



entry	X^1, X^2	conversion (%)	NMR yield (%)[b]	yield (%)[c]
1	F, F (**3.1a**)	100%	90%	80%
2	H, F (**3.1a'**)	8%	0%	0%
3	H, H (**3.1a"**)	0%	0%	0%

[a] Standard reaction conditions: **3.1a–a"** (1.0 equiv), $Pd(PPh_3)_4$ (2.5 mol%), *o*-xylene (0.05 M), 120 °C, 15 h. The reported data represents an average of two independent experiments. [b] The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene and fluorobenzene (**3.1a** and **3.1a'**) and by ^1H NMR using CH_2Br_2 (**3.1a"**) as an internal standard. [c] Yield of isolated product.

3.5 Conclusion

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

[1] (a) Bégué, J.-P.; Bonnet-Delpon, D. *Inhibition of Enzymes by Fluorinated Compounds. Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: Hoboken, NJ, **2008**; Chapter 7, pp. 246–256. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: West Sussex, U.K., **2009**; pp 29–31.

[2] (a) Guthrie, J. P. "Carbonyl Addition Reactions. Factors Affecting the Hydrate-Hemiacetal and Hemiacetal-Acetal Equilibrium Constants" *Can. J. Chem*. **1975**, *53*, 898–905. (b) Braendlin, H. P.; McBee, E. T. in *Advances in Fluorine Chemistry*, Stacey, M.; Tatlow, J. C.; Sharp, A. G., Eds.; Butterworths, London, **1993**; Vol. 3, p. 1.

[3] (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. "Fluoro Ketone Inhibitors of Hydrolytic Enzymes" *Biochemistry* **1985**, *24*, 1813–1817. (b) Corte, J. R.; Fang, T.; Decicco, C. P.; Pinto, D. J. P.; Rossi, K. A.; Hu, Z.; Jeon, Y.; Quan, M. L.; Smallheer, J. M.; Wang, Y.; Yang, W. (Bristol-Myers Squibb Company) "Preparation of Tetrazolylphenyldiazatricyclooctadecapentaenylacrylamide Derivatives and Analogs for Use as Factor XIa Inhibitors" WO 2011100401, **2011**.

[4] (a) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. "Fluoro Ketone Containing Peptides as Inhibitors of Human Renin" *J. Med. Chem*. **1987**, *30*, 1617–1622. (b) Sham, H. L.; Wideburg, N. E.; Spanton, S. G.; Kohlbrenner, W. E.; Betebenner, D. A.; Kempf, D. J.; Norbeck, D. W.; Plattner, J. J.; Erickson, J. W. "Synthesis of (*2S*,*5S*,*4R*)-2,5-Diamino-3,3-difluoro-1,6-diphenylhydroxyhexane: the Core Unit of a Potent HIV Proteinase Inhibitor" *J. Chem. Soc. Chem. Commun*. **1991**, 110–112. (c) Faeh, C.; Mathys, R.; Hardegger, L. A.; Meyer, S.; Bur, D.; Diederich, F. "Enantiomerically Pure and Highly Substituted Alicyclic α,α-Difluoro Ketones: Potential Inhibitors for Malarial Aspartic Proteases, the Plasmepsins" *Eur. J. Org. Chem*. **2010**, 4617–4629.

[5] (a) Lefebvre, O.; Brigaud, T.; Portella, C. "Mixed Organofluorine-Organosilicon Chemistry. 10. Allylation and Benzylation of Difluoroenoxysilanes. Application to the Synthesis of *gem*-Difluoroterpene Analogues" *Tetrahedron* **1999**, *55*, 7233–7242. (b) Ginzburg, R.; Ambizas, E. M. "Clinical Pharmacology of Lubiprostone, a Chloride Channel Activator in Defecation Disorders" *Expert Opin Drug Metab Toxicol*. **2008**, *4*, 1091–1097. (c) 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 γ-Aminobutyric Acid Type B ($GABA_B$) Receptor" *J. Med. Chem*. **2013**, *56*, 2456–2465. (d) Dreyer, G. B.; Metcalf, B. W. "α,α-Difluoro Ketone Inhibitors of HMG CoA Reductase" *Tetrahedron Lett*. **1988**, *29*, 6885–6888. (e) Hamer, R. L.; Freed, B.; Allen, R. C. (Hoechst-Roussel Pharmaceuticals) "Preparation of Phenylethanones as Analgesics and Drugs for Treatment of Memory Dysfunction" US 5006563, **1991**. (f) Banville, J.; Remillard, R.; Balasubramanian, N.; Bouthillier, G.; Martel, A. (Bristol-Myers Squibb) "Preparation of Phenolic and Thiophenolic Ethers and Their Derivs. as Cytosolic Phospholipase A2 Inhibitors" US 20020037875, **2002**. (g) Shimada, Y.; Taniguchi, N.; Matsuhisa, A.; Sakamoto, K.; Yatsu, T.; Tanaka, A. "Highly Potent and Orally Active Non-Peptide Arginine Vasopressin Antagonists for Both V1A and V2 Receptors: Synthesis and Pharmacological Properties of 4'-[(4,4-Difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]-2-phenylbenzanilide Derivatives" *Chem. Pharm. Bull*. **2000**, *48*, 1644–1651.

[6] (a) Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruett, S. T.,; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, G. P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C. "Discovery of a Fluorinated Enigmol Analog with Enhanced *in vivo* Pharmacokinetic and Anti-tumor Properties" *ACS Med. Chem. Lett*. **2016**, *7*, 537–542. (b) Henschke, J. P.; Liu, Y.; Xia, L.; Chen, Y.-F. (ScinoPharm (Kunshan) Biochemical Technology) "Processes for Preparation and Purification of Lubiprostone" WO 2012048447, **2012**. (c) Sham, H. L.; Rempel, C. A.; Stein, H.; Cohen, J. "Synthesis of 6(*S*)-Amino-7-cyclohexyl-4,4-difluoro-3(*R*),5(*R*)-dihydroxy-2-methylheptane, A Novel Dipeptide Mimic" *J. Chem. Soc., Chem. Commun*. **1990**, 904–905. (d) Dahlgren, M. K.; Oeberg, C. T.; Wallin, E. A.; Janson, P. G.; Elofsson, M. "Synthesis of 2-(2-Amino-pyrimidine)-2,2-difluoroethanols as

Potential Bioisosters of Salicylidene Acylhydrazides" *Molecules* **2010**, *15*, 4423–4438. (e) Hoekstra, W. J.; Garvey, E. P.; Moore, W. R.; Rafferty, S. W.; Yates, C. M.; Schotzinger, R. J. "Design and Optimization of Highly-Selective Fungal CYP51 Inhibitors" *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3455–3458. (f) Qiu, Z.-M.; Burton, D. J. "Synthesis of α,α-Difluoro-Functionalized Ketones" *J. Org. Chem*. **1995**, *60*, 5570–5578.

[7] (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. "Facile Preparation of Di- and Monofluoromethyl Ketones from Trifluoromethyl Ketones *via* Fluorinated Enol Silyl Ethers" *J. Fluorine Chem*. **2001**, *112*, 357–362. (b) Chorki, F.; Grellepois, F.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J.-P. "Fluoro Artemisinins: Difluoromethylene Ketones" *J. Org. Chem*. **2001**, *66*, 7858–7863. (c) Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T. "Synthesis of β-Amino-α,α-difluoro Ketones by Reactions of 1,1-Difluorovinyl Methyl Ethers with *N*-Acyliminium Intermediates" *Tetrahedron Lett*. **1996**, *37*, 1061–1064. (d) Kashikura, W.; Mori, K.; Akiyama, T. "Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of β-Amino-α,α-difluoro Carbonyl Compounds" *Org. Lett*. **2011**, *13*, 1860–1863. (e) Berber, H.; Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. "Reactions of Difluoroenoxysilanes with Glycosyl Donors: Synthesis of Difluoro-C-glycosides and Difluoro-C-disaccharides" *Chem. Eur. J*. **2001**, *7*, 903–909. (f) Whitten, J. P.; Barney, C. L.; Huber, E. W.; Bey, P.; McCarthy, J. R. "Convenient Synthetic Access to β,β-Difluoro-γ-keto-α-amino Acids. Application to the Synthesis of a Potential Inhibitor of Kynureninase" *Tetrahedron Lett*. **1989**, *30*, 3649–3652. (g) Shi, G.-Q.; Cai, W.-L. "3,3-Difluoro-2-ethoxy-2-propenol: Preparation and Utility as a Novel Synthon of α,α-Difluoroketones" *Synlett* **1996**, 371–372. (h) Guo, Y.; Shreeve, J. M. "Effect of Fluorine on Palladium-Catalyzed Cross-Coupling Reactions of Aryl Bromides with Trifluoromethyl Aryl Ketones *via* Difluoroenol Silyl or Monofluoroenol Silyl Ethers" *Chem. Commun*. **2007**, 3583–3585. (i) Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. "Oxidative Cross-Coupling of β,β-Difluoroenol Silyl Ethers with Nucleophiles: A Dipole-Inversion Method to Difluoroketones" *Org. Lett*. **2004**, *6*, 2733–2736. (j) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. "Difluorinated Danishefsky's Diene: A Versatile C_4 Building Block for the Fluorinated Six-Membered Rings" *Org. Lett*. **2001**, *3*, 3103–3105. (k) Wu, Y.-B.; Lu, G.-P.; Zhou, B.-J.; Bu, M.-J.; Wan, L.; Cai, C. "Visible-Light-Initiated Difluoromethylation of Arene Diazonium Tetrafluoroborates" *Chem. Commun*. **2016**, 52, 5965–5968.

[8] (a) Biju, P. "New Methodology for the Synthesis of α,α-Difluoroketones" *Synth. Commun*. **2008**, *38*, 1940–1945. (b) Makriyannis, A.; Nikas, S. P.; Alapafuja, S. O.; Shukla, V. G. (University of Connecticut, USA) "Preparation of Cyclic Compounds as Therapeutic Fatty Acid Amide Hydrolase Inhibitors that Modulate the Cannabinergic System" WO 2008013963, **2008**. (c) Yu, K.-L.; Mansuri, M. M.; Starrett Jr, J. E. "A Novel Synthesis of 1,2-Diaryl-2,2-difluoroethanones" *Tetrahedron Lett*. **1994**, *35*, 8955–8956. (d) Hoekstra, W. J.; Schotzinger, R. J. (Viamet Pharmaceuticals, Inc., USA) "Preparation of Heteroaryl Substituted Propan-2-ol Compds. as Metalloenzyme Inhibitors" WO 2012177728, **2012**.

[9] (a) Differding, E.; Ruegg, G. M.; Lang, R. W. "Selective Mono- and Difluorination of Enolates" *Tetrahedron Lett*. **1991**, *32*, 1779–1782. (b) Singh, R. P.; Shreeve, J. M. "Recent Highlights in Electrophilic Fluorination with 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate)" *Acc. Chem. Res*. **2004**, *37*, 31–44. (c) Pravst, I.; Zupan, M.; Stavber, S. "Efficient Synthesis of α,α-Difluoro Ketones Using Selectfluor F-TEDA-BF_4" *Synthesis* **2005**, 3140–3146. (d) Ramírez, J.; Fernandez, E. "Convenient Synthesis of α,α-Difluorinated Carbonyl Compounds from Alkynes through a Fluoro-Deboronation Process" *Synthesis* **2005**, 1698–1700. (e) Zupan, M.; Iskra, J.; Stavber, S. "Regioselective Conversions of 1-Phenyl-Substituted Acetylenes to α,α-Difluoro Ketones with "F-TEDA-BF_4"" *J. Org. Chem*. **1995**, *60*, 259–260. (f) Stavber, S.; Zupan, M. "Effective Synthesis of α,α-Difluoro Ketones Using Accufluor (NFTh) Fluorinating Reagent" *Synlett* **1996**, 693–694. (g) Patrick, T. B.; Darling, D. L. "Fluorination of Activated Aromatic Systems with Cesium Fluoroxysulfate" *J. Org. Chem*. **1986**, *51*, 3242–3244.

[10] (a) Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. "Geminal Fluorination of Diazo Compounds" *J. Org. Chem*. **1981**, *46*, 3917–3918. (b) Rozen, S.; Zamir, D. "Conversion of the Carbonyl Group to CF_2 Using

Iodine Monofluoride (IF)" *J. Org. Chem*. **1991**, *56*, 4695–4700. (c) McCarthy, P. A.; Wint, L. T.; Diaz, C. L. "Synthesis of α,α-Difluoroketones: Novel Synthesis of α,α-Difluoroketones from α,α-Difluoroacylsilanes" *Bioorg. Med. Chem. Lett*. **1992**, *2*, 119–122. (d) Qiu, Z. M.; Burton, D. J. "A General Route to α,α-Difluoroketones" *Tetrahedron Lett*. **1993**, *34*, 3239–3242. (e) Garayt, M. R.; Percy, J. M. "A Direct and Useful Route to Difluoroacylsilanes and Difluoroacylstannanes and Their Potential for the Generation of Structurally Diverse Difluoroketones" *Tetrahedron Lett*. **2001**, *42*, 6377–6380. (f) Fukuhara, T.; Hara, S. "Desulfurizing Difluorination Reaction of Benzyl Sulfides Using IF_5" *Synlett* **2009**, 198–200. (g) Guo, C.; Wang, R.-W.; Qing, F.-L. "Palladium Catalyzed Direct α-Arylation of α,α-Difluoroketones with Aryl Bromides" *J. Fluorine Chem*. **2012**, *143*, 135–142. (h) Ge, S.; Chaladaj, W.; Hartwig, J. F. "Pd-Catalyzed α-Arylation of α,α-Difluoroketones with Aryl Bromides and Chlorides. A Route to Difluoromethylarenes" *J. Am. Chem. Soc*. **2014**, *136*, 4149–4152. (i) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. "Difluorohomologation of Ketones" *Org. Lett*. **2015**, *17*, 760–763. (j) Decostanzi, M.; Campagne, J.-M.; Leclerc, E. "Low-Temperature Intermolecular Addition of RCF_2Li Compounds to Various Carbonyl Electrophiles for a Practical Synthesis of CF_2-Containing Building Blocks" *Synthesis* **2016**, *48*, 3420–3428.

[11] (a) Harrington, P. E.; Li, L.; Tius, M. A. "Difluorocyclopentenone Synthesis" *J. Org. Chem*. **1999**, *64*, 4025–4029. (b) Suda, M. "Radical Addition Reactions on 1,1-Difluoro-1-olefins" *Tetrahedron Lett*. **1981**, *22*, 2395–2396.

[12] (a) Stolz, D.; Kazmaier, U. "Metal Enolates as Synthons in Organic Chemistry: In *Chemistry of Metal Enolates*" (Ed.: Zabicky, J.) John Wiley & Sons, Ltd., London, UK, **2009**, Chapter 7, 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 (Second Edition)* (Eds.: Knochel, P.; Molander, G. A.) Elsevier, English, **2014**, *Vol. 3*, pp 1–55.

[13] (a) Yamana, M.; Ishihara, T.; Ando, T. "A Convenient Synthesis of 2,2-Difluoro Enol Silyl Ethers from Chlorodifluoromethyl Ketones" *Tetrahedron Lett*. **1983**, *24*, 507–510. (b) Kuroboshi, M.; Ishihara, T. "An Efficient and General Method for the Reformatsky-Type Reaction of Chlorodifluoromethyl Ketones with Carbonyl Compounds Giving α,α-Difluoro-β-hydroxy Ketones" *Bull. Chem. Soc. Jpn*. **1990**, *63*, 428–437. (c) Liu, Y.-L.; Zhou, J. "Organocatalytic Asymmetric Synthesis of 3-Difluoroalkyl 3-Hydroxyoxindoles" *Chem. Commun*. **2012**, *48*, 1919–1921.

[14] (a) Uneyama, K. Fundamentals in *Organic Fluorine Chemistry. Organofluorine Chemistry*, Blackwell, Oxford, **2006**, Chapter 1, p10. (b) Qian, C.-P.; Nakai, T. "Ketone Perfluoroenolates: Regioselective and Stereoselective Synthesis, Unique Reactivities, and Electronic Properties" *J. Am. Chem. Soc*. **1990**, *112*, 4602–4604.

[15] Qian, C.-P.; Nakai, T. "Perfluoro-Enolate Chemistry: Facile Generation and Unique Reactivities of Metal F-1-Propen-2-olates" *Tetrahedron Lett*. **1988**, *29*, 4119–4122.

[16] (a) Brigaud, T.; Doussot, P.; Portella, C. "Synthesis of Difluoroenoxysilanes from Acylsilanes and Trifluoromethyltrimethylsilane (TFMTMS). Dramatic Effect of the Catalytic Fluoride Source" *J. Chem. Soc., Chem. Commun.* **1994**, 2117–2118. (b) Lefebvre, O.; Brigaud, T.; Portella, C. "Mixed Organofluorine-Organosilicon Chemistry. 10. Allylation and Benzylation of Difluoroenoxysilanes. Application to the Synthesis of *gem*-Difluoroterpene Analogues" *Tetrahedron* **1999**, *55*, 7233–7242. (c) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. "A New Finding in Selective Baeyer-Villiger Oxidation of α-Fluorinated Ketones; a New and Practical Route for the Synthesis of α-Fluorinated Esters" *Tetrahedron* **2003**, *59*, 1547–1552.

[17] (a) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. "Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions" *Chem. Rev*. **2011**, *111*, 1846–1913. (b) Recio III, A.; Tunge, J. A. "Regiospecific Decarboxylative Allylation of Nitriles" *Org. Lett*. **2009**, *11*, 5630–5633. (c) Jana, R.; Partridge, J. J.; Tunge, J. A. "Migratory Decarboxylative Coupling of Coumarins: Synthetic and Mechanistic Aspects" *Angew. Chem. Int. Ed*. **2011**, *50*, 5157–5161.

[18] We acknowledged Niusha Sharifi for the initial screening of decarboxylative benzylation reactions of α,α-difluoroketone enolates.
[19] Surry, D. S.; Buchwald, S. L. "Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide" *Chem. Sci*. **2011**, *2*, 27–50.
[20] Hansch, C.; Leo, A.; Taft, R. W. "A Survey of Hammett Substituent Constants and Resonance and Field Parameters" *Chem. Rev*. **1991**, *91*, 165–195.
[21] (a) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. "Palladium-Catalyzed Substitution of Esters of Naphthylmethanols, 1-Naphthylethanols, and Analogs by Sodium Dimethyl Malonate. Stereoselective Synthesis from Enantiomerically Pure Substrates" *Tetrahedron* **1995**, *51*, 3235–3246. (b) Torregrosa, R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. "Decarboxylative Benzylations of Alkynes and Ketones" *J. Am. Chem. Soc*. **2010**, *132*, 9280–9282.
[22] Trying to prepare the difluorinated enolate-bound palladium-π-benzyl complex failed. However, a C-bound fluorinated enolate intermediate [*trans*-$PdCl(PPh_3)_2(CF_2COPh)$] was confirmed by X-ray crystallography. According to literature reports regarding coordination modes of palladium enolates, enolates prefer to coordinate to Pd through the carbon atom. [1) *Organometallics*. **1993**, *12*, 4899; 2) *J. Chem. Soc. Dalton Trans*. **1995**, 3093; 3) *J. Am. Chem. Soc*. **2001**, *123*, 5816; 4) *Organometallics*. **2004**, *23*, 3398; and 5) *Organometallics*. **1990**, *9*, 30.] However, the less common O-bound-Pd-enolates exist only for specified examples that bear multiple bulky substituents or chelating phosphine groups on the substrates. [1) *Inorg. Chem*. **1988**, *27*, 2279; 2) *J. Chem. Soc. Chem. Commun*. **1987**, *7*, 488; 3) *Tetrahedron Lett*. **1980**, *21*, 2873.] For these reasons, we draw C-bound fluorinated enolate-palladium-π-benzyl complex, but still cannot completely exclude out the existence of the O-bound enolate.
[23] Trost, B. M.; Czabaniuk, L. C. "Structure and Reactivity of Late Transition Metal η^3-Benzyl Complexes" *Angew. Chem. Int. Ed*. **2014**, *53*, 2826–2851.
[24] Bordwell, F. G. "Equilibrium Acidities in Dimethyl Sulfoxide Solution" *Acc. Chem. Res*. **1988**, *21*, 456–463.
[25] Hine, J.; Mahone, L. G.; Liotta, C. L. "α-Fluoro and α-Alkoxy Substituents as Deactivators in Carbanion Formation" *J. Am. Chem. Soc*. **1967**, *89*, 5911–5920.
[26] Substrates bearing heterocycle-type benzylic moieties, such as pyrazoles and indoles, are not included in this thesis. Please see *Angew. Chem. Int. Ed*. **2016**, *55*, 9080–9083 for the details.

Chapter 3 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 3

Table of Contents

General Information

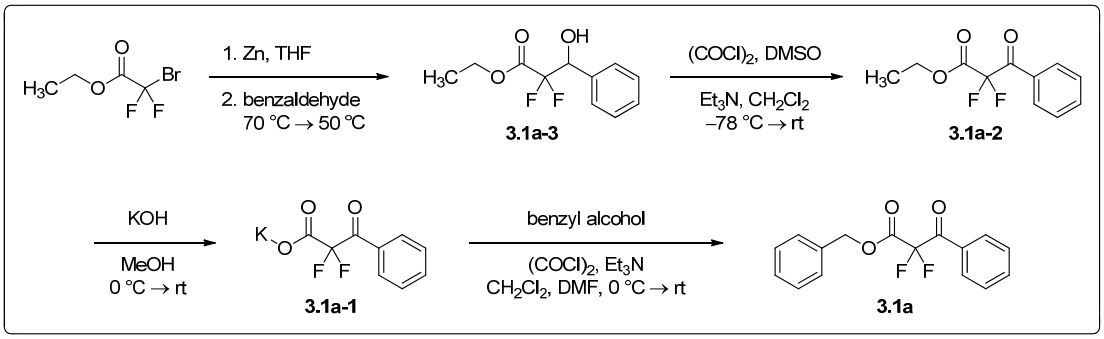
Unless otherwise noted, reactions were performed under an atmosphere of N_2 using oven-dried glassware. Palladium-catalyzed reactions were performed in 20 mL pressure-resistant scintillation vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with $KMnO_4$, anisaldehyde or iodine. Column chromatography was conducted using an automated system. ^{19}F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. *o*-Xylene (anhydrous) and $Pd(PPh_3)_4$ (reagent grade, 99%) were purchased from Sigma Aldrich. Solvents including DMF, PhMe, CH_2Cl_2, THF, MeOH were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual $CHCl_3$ in the NMR solvent ($CDCl_3$: $\delta = 7.27$ ppm or DMSO-d_6: $\delta = 2.50$ ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak ($CDCl_3$: $\delta = 77.23$ ppm or DMSO-d_6: $\delta = 39.51$ ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ^{19}F NMR chemical shifts (δ) are reported in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity

(s = singlet, d = doublet, t = triplet, q = quartet, p = pent, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier^{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 at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

Preparation of Compound 3.1a



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

An oven-dried three-neck flask was charged with activated Zn (6.40 g, 98.4 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with $N_{2(g)}$ three times. Dry THF (0.10 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.50 mL, 5.8 mmol) under $N_{2(g)}$. To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of aldehyde (5.0 mL, 49 mmol) and ethyl bromodifluoroacetate (6.4 mL, 49 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to 0 °C, and 1 N $HCl_{(aq)}$ was added until the residual Zn was consumed (roughly 100 mL). The reaction mixture was warmed to rt, and transferred to a separation funnel. The phases were separated, and

the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 15%) for elution to provide the compound **3.1a-3** as a colorless oil (10.5 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.39 (m, 5 H), 5.18 (ddd, *J* = 15.6, 8.0, 5.2 Hz, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.66 (d, *J* = 5.2 Hz, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.4 (dd, *J* = 263.2, 15.4 Hz, 1 F), –113.9 (dd, *J* = 263.2, 7.9 Hz, 1 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_{12}F_2O_3Na$ $[M+Na]^+$ 253.0652, found 253.0663. Spectroscopic data matched that from the previous report.[1]

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

An oven-dried three-neck flask was equipped with a liquid addition funnel, a three-way valve and two rubber septa, evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (130 mL) and oxalyl chloride (6.1 mL, 71 mmol) were added sequentially at rt, and the reaction solution was cooled to –78 °C. A solution of anhydrous DMSO (6.7 mL, 94 mmol) in dry CH_2Cl_2 (13 mL) was added dropwise at –78 °C, and then the reaction solution was stirred at this temperature for 1 h. Next, a solution of **3.1a-3** (5.42 g, 23.5 mmol) dissolved in dry CH_2Cl_2 (13 mL) was added dropwise at –78 °C, and then the resulting reaction solution was stirred at this temperature for 1 h. Et_3N (0.020 L, 0.14 mol) was added dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was gradually warmed to rt, and stirred at rt for 2 h. H_2O (100 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to afford the compound **3.1a-2** as a as a light yellow oil (4.40 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 7.6 Hz, 2 H), 7.71–7.67 (m, 1 H), 7.56–7.52 (m, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.33 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.6 (s, 2 F). HRMS (ESI, *m/z*): calcd for

$C_{11}H_{10}F_2O_3Na$ $[M+Na]^+$ 251.0496, found 251.0490. Spectroscopic data matched that from the previous report.[2]

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

A one-neck round-bottom flask was charged with **3.1a-2** (3.10 g, 13.6 mmol), and MeOH (7.0 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.760 g, 13.6 mmol) dissolved in MeOH (7.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred at rt for 6 h. MeOH was removed under reduced pressure. EtOAc (5 mL) and ether (5 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried *in vacuo* to give the compound **3.1a-1** as a colorless solid (2.72 g, 84%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.00 (d, J = 8.0 Hz, 2 H), 7.65 (t, J = 7.6 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 189.6 (t, J = 27.5 Hz), 162.4 (t, J = 23.8 Hz), 133.8, 132.6, 129.2, 128.5, 111.3 (t, J = 261.9 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –105.2 (s, 2 F). IR (film) 3061, 1720, 1697, 1682, 1645, 1599, 1450, 1412, 1381, 1281, 1169, 1132, 1101, 922, 912, 816, 729, 708, 685, 584 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_9H_5F_2K_2O_3$ $[M+K]^+$ 276.9481, found 276.9492. mp 154–155 ºC decomposed.

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

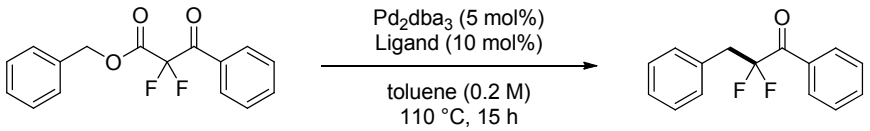
An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (4.3 g, 18 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (0.090 L) and DMF (0.46 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (1.4 mL, 17 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. Next, benzyl alcohol (1.5 mL, 15 mmol) was added dropwise at 0 °C followed by dropwise addition of Et_3N (4.2 mL, 30 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. H_2O (15 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The

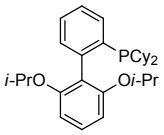
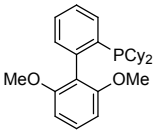
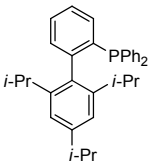
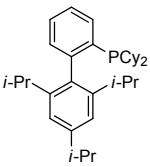
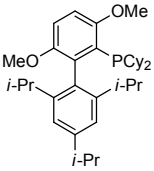
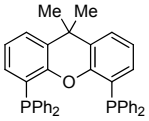
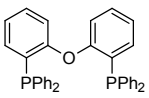
crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **3.1a** as a colorless oil (3.5 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.36–7.30 (m, 5 H), 5.35 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 135.3, 133.9, 131.1 (t, *J* = 2.5 Hz), 130.1 (t, *J* = 2.5 Hz), 129.2, 129.1, 128.9, 128.6, 110.0 (t, *J* = 263.1 Hz), 69.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (s, 2 F). IR (film) 3068, 3036, 1778, 1715, 1699, 1597, 1499, 1450, 1381, 1308, 1259, 1157, 1101, 1080, 920, 798, 746, 712, 696, 687, 579 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_2O_3Na$ $[M+Na]^+$ 313.0652, found 313.0666.

Initial Screening and Optimization of Reaction Conditions[3]

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

Table S1. Screening Conditions of Pd_2dba_3-Catalyzed Decarboxylative Difluorobenzylation: Ligands[a,b,c]

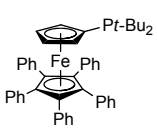


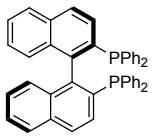
						
66%	69%	66%	53%	48%	44%	50%
RuPhos	SPhos	PhXPhos	XPhos	BrettPhos	Xantphos	DPEPhos

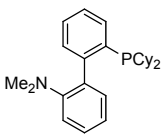
[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

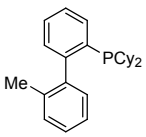
[b] The conversion for all reactions above was more than 99%.

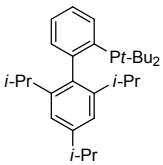
Other ligands screened that produced < 15% product by GC are shown below.

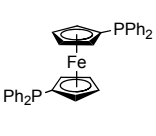

QPhos

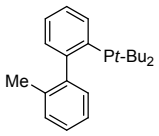

rac-BINAP

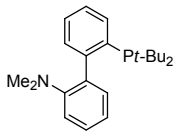

DavePhos

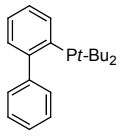

MePhos

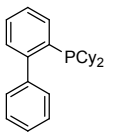

t-BuXPhos

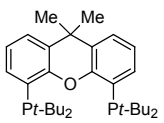

dppf

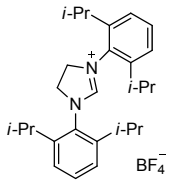

t-BuMePhos

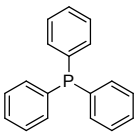

t-BuDavePhos

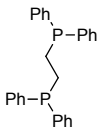

JohnPhos

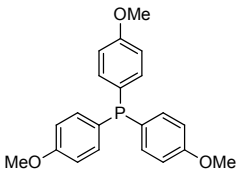

CyJohnPhos

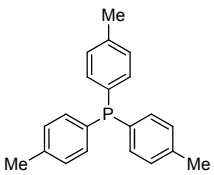

t-BuXantphos

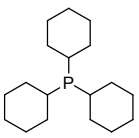

1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate

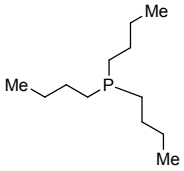

PPh_3

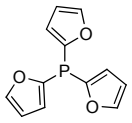

dppe

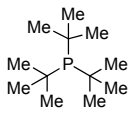

Tris(4-methoxyphenyl) phosphine

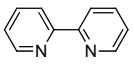

Tri(*p*-tolyl)phosphine

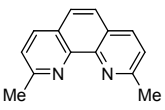

PCy_3

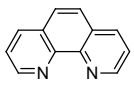

P*n*-Bu_3

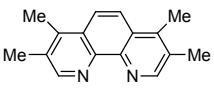

Tri(2-furyl)phosphine


P*t*-Bu_3


2,2'-Bipyridine

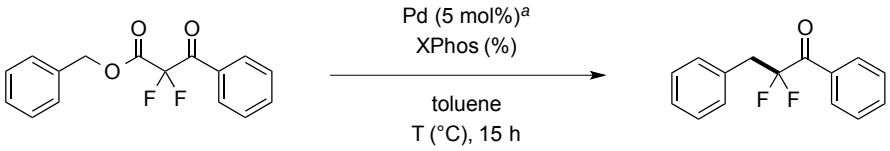

Neocuproine


1,10-phenanthroline


3,4,7,8-Tetramethyl-1,10-phenanthroline

[c] We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation reactions.

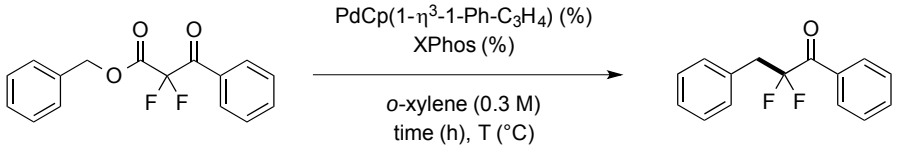
Table S2. Screening Conditions of Pd-Catalyzed Decarboxylative Difluorobenzylation: Pd Sources, Temperature and Concentration



entry	Pd	XPhos (%)	T (°C)	conc. (M)	yield (%)[b]	conv (%)
1	Pd_2dba_3	10	110	0.2	43	100
2	$PdCl_2$	15	110	0.2	7	56
3	$Pd(OAc)_2$	15	110	0.2	43	100
4	$Pd(TFA)_2$	15	110	0.2	21	95
5	$Pd(CH_3CN)_2Cl_2$	15	110	0.2	23	78
6	$Pd(acac)_2$	15	110	0.2	0	35
7	$Pd(\eta^3\text{-}C_2H_5)_2Cl_2$	15	110	0.2	37	100
8	$Pd(OAc)_2$	15	100	0.2	41	100
9	$Pd(OAc)_2$	15	90	0.2	36	99
10[c]	$Pd(OAc)_2$	15	100	0.2	42	100
11[d]	$Pd(OAc)_2$	15	100	0.2	13	100
12	$Pd(OAc)_2$	15	110	0.5	36	99
13	$Pd(OAc)_2$	15	110	0.1	46	100

[a] Pd (5 mol%) indicates dimeric Pd (2.5 mol%) and monomeric Pd (5 mol%).
[b] Yields were determined by GC using dodecane as an internal standard.
[c] Solvent: 1,4-dioxane
[d] Solvent: DMF

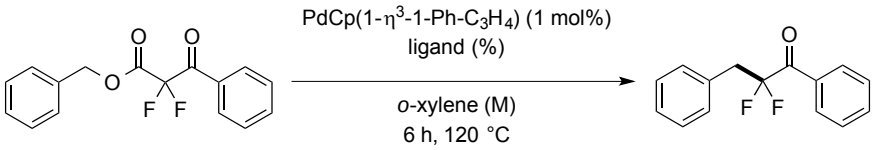
Table S3. Screening Conditions of PdCp(1-η³-1-Ph-C_3H_4)-Catalyzed Decarboxylative Difluorobenzylation: Catalyst Loading, Temperature and Reaction Time



entry	Pd (%)	XPhos (%)	T (°C)	time (h)	yield (%)[a]	conv (%)
1	5	10	120	6	54	100
2	3	6	120	6	62	100
3	2	4	120	6	69	100
4	1	2	120	6	70	100
5	1	2	120	15	64	100
6	1	2	120	24	65	100
7	1	2	140	6	73	100
8	**1**	**2**	**130**	**6**	**72**	**100**
9	1	2	110	6	64	100
10	1	2	100	6	50	90

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

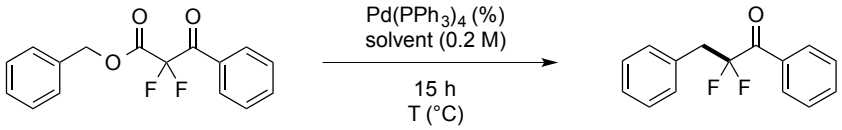
Table S4. Screening Conditions of PdCp(1-η^3-1-Ph-C_3H_4)-Catalyzed Decarboxylative Difluorobenzylation: Concentration and Ligands



entry	ligand (%)	conc. (M)	yield (%)[a]	conv (%)
1	XPhos (2)	0.2	73	100
2	**XPhos (2)**	**0.1**	**77**	**100**
3	XPhos (2)	0.05	19	22
4	XPhos (2)	0.5	63	100
5	XPhos (2)	1.0	58	100
6	RuPhos (2)	0.1	43	61
7	SPhos (2)	0.1	35	48
8	**PhXPhos (2)**	**0.1**	**77**	**100**
9	*t*BuXPhos (2)	0.1	0	0
10	4Me*t*BuXPhos (2)	0.1	0	0
11	**PPh_3 (3)**	**0.1**	**75**	**77**
12	P(*o*-Tol)$_3$ (2)	0.1	0	0
13	P(*p*-C_6H_4OMe)$_3$ (2)	0.1	18	28
14	P(2-furyl)$_3$ (2)	0.1	0	0
15	PCy_3 (2)	0.1	0	0

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

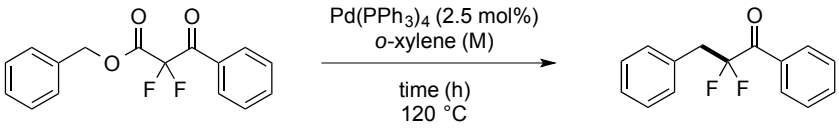
Table S5. Optimization of $Pd(PPh_3)_4$-Catalyzed Decarboxylative Difluorobenzylation-Screening Conditions: Catalyst Loading, Solvent and Temperature



entry	Pd (%)	solvent	T (°C)	yield (%)[a]	conv (%)
1	5	toluene	110	45	100
2	5	DME	100	4	100
3	5	2-Me-THF	80	10	98
4	5	DMF	80	1	94
5	5	1,4-dioxane	100	41	100
6	5	CH_3CN	80	0	69
7	5	*o*-xylene	120	78	100
8	5	*o*-xylene	130	76	100
9	5	*o*-xylene	140	74	100
10	**2.5**	***o*-xylene**	**120**	**95 (74)**	**100**
11	1.0	*o*-xylene	120	58	100
12	10	*o*-xylene	120	66	100

[a] Yields were determined by GC using dodecane as an internal standard. The value in parentheses was ^{19}F NMR yields using α,α,α-trifluorotoluene as an internal standard.

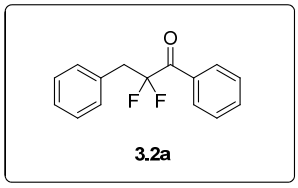
Table S6. Optimization of $Pd(PPh_3)_4$-Catalyzed Decarboxylative Difluorobenzylation-Screening Conditions: Concentration and Reaction Time



entry	conc. (M)	time (h)	yield (%)[a]	conv (%)
1	1.0	15	55	100
2	0.5	15	66	100
3	0.3	15	70	100
4	0.1	15	75	100
5	**0.05**	**15**	**87**	**100**
6	0.05	6	76	100
7	0.05	10	83	100
8	0.05	24	88	100

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

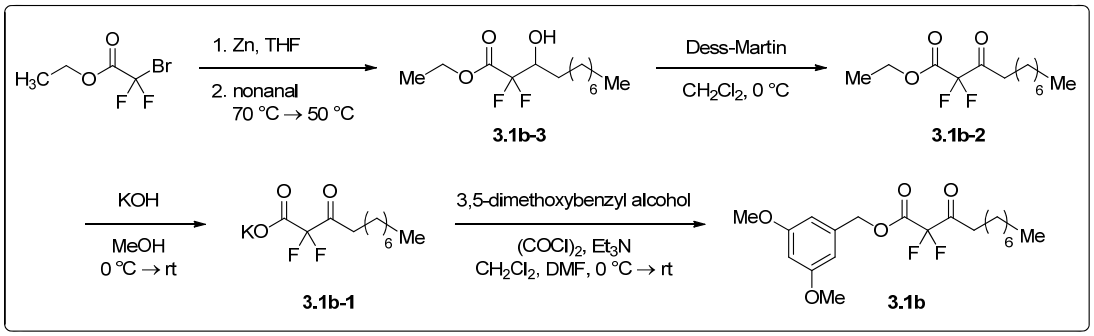
Characterization of Compound 3.2a



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

^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 7.6 Hz, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.32 (br, 5 H), 3.53 (t, *J* = 17.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.7 (t, *J* = 30.6 Hz), 134.4, 132.3 (t, *J* = 2.5 Hz), 131.5 (t, *J* = 3.1 Hz), 131.1, 130.3 (t, *J* = 3.7 Hz), 128.8, 128.6, 127.8, 118.6 (t, *J* = 253.1 Hz), 40.3 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.6 (t, *J* = 16.9 Hz, 2 F). IR (film) 3063, 3032, 2937, 1701, 1597, 1497, 1450, 1279, 1173, 1115, 1084, 1049, 1032, 943, 901, 727, 715, 698, 669, 600 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{12}F_2ONa$ $[M+Na]^+$ 269.0754, found 269.0742. m.p. 45 °C. Spectroscopic data matched that from the previous report.[4]

Experimental Procedures and Characterization of Compounds in Scheme 3.13



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

An oven-dried three-neck flask was charged with activated Zn (3.20 g, 49.2 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with $N_{2(g)}$ three times. Dry THF (0.05 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.25 mL, 2.9 mmol) under $N_{2(g)}$. To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of nonyl aldehyde (4.3 mL, 25 mmol) and ethyl bromodifluoroacetate (3.2 mL, 25 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to rt, and the residual Zn was filtered through a pad of celite and washed with EtOAc. The filtrate was acidified with 1 N $HCl_{(aq)}$ to pH 3–4, and the solution was transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (5% to 10%) for elution to provide the compound **3.1b-3** as a colorless liquid (4.0 g, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.37 (q, *J* = 7.2 Hz, 2 H), 4.08–3.97 (m, 1 H), 1.98 (d, *J* = 7.2 Hz, 1 H), 1.72–1.65 (m, 1 H), 1.64–1.50 (m, 2 H), 1.43–1.27 (m, 14 H), 0.89 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9 (t, *J* = 31.9 Hz), 114.9 (dd, *J* = 255.0, 252.5 Hz), 72.0 (dd, *J* = 26.2, 25.0 Hz), 63.2, 32.0, 29.6, 29.5, 29.4, 29.3, 25.4, 22.9,

14.3, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –122.4 (dd, *J* = 267.0, 15.0 Hz, 1 F), –115.0 (dd, *J* = 267.0, 7.5 Hz, 1 F). IR (film) 3477, 2957, 2928, 2856, 1759, 1468, 1396, 1375, 1315, 1217, 1122, 1092, 856, 783, 721 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{13}H_{24}F_2O_3Na$ $[M+Na]^+$ 289.1591, found 289.1581.

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

Dess-Martin periodinane (7.38 g, 17.4 mmol) was added into a solution of compound **3.1b-3** (3.56 g, 13.4 mmol) dissolved in CH_2Cl_2 (0.100 L) at 0 °C, and the solution was stirred at rt for 2 h. The solvent was removed under reduced pressure, and the residue was stirred in EtOAc / hexanes (1:10, 100 mL) and sonicated. The white solid was filtered through a pad of celite, and washed with EtOAc / hexanes (1:10). The filtrate was concentrated to provide the title compound **3.1b-2** as a colorless liquid (3.49g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (q, *J* = 7.2 Hz, 2 H), 2.74 (t, *J* = 7.2 Hz, 2 H), 1.66 (p, *J* = 7.0 Hz, 2 H), 1.38–1.28 (m, 13 H), 0.89 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (t, *J* = 27.5 Hz), 161.7 (t, *J* = 30.0 Hz), 108.4 (t, *J* = 262.5 Hz), 63.9, 36.8, 32.0, 29.4, 29.2, 29.0, 22.8, 22.6, 14.3, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –113.9 (s, 2 F). IR (film) 2957, 2930, 2858, 1782, 1747, 1468, 1402, 1373, 1313, 1203, 1140, 1014, 959 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{13}H_{22}F_2O_3Na$ $[M+Na]^+$ 287.1435, found 287.1421.

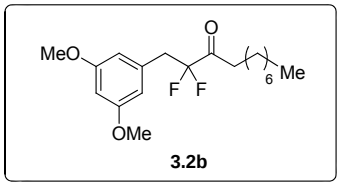
potassium 2,2-difluoro-3-oxoundecanoate (3.1b-1)

A one-neck round-bottom flask was charged with **3.1b-2** (2.84 g, 10.7 mmol), and MeOH (18 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.600 g, 10.7 mmol) dissolved in MeOH (5.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred for 6 h. The solvent was removed under reduced pressure. Ether (15 mL) was added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried *in vacuo* to give the compound **3.1b-1** as an off-white solid (2.4 g, 82%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.57 (t, *J* = 7.2 Hz, 2 H), 1.46 (p, *J* = 7.0 Hz, 2 H), 1.29–1.23 (m, 10 H), 0.85 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 201.6 (t, *J* = 26.9 Hz), 162.1 (t, *J* = 25.0 Hz), 111.0 (t, *J* = 262.5 Hz), 36.6, 31.3, 28.8, 28.6, 28.4, 22.5, 22.1, 14.0. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –111.4 (s,

2 F). IR (film) 2955, 2922, 2854, 1742, 1661, 1468, 1398, 1194, 1124, 1082, 818 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{11}H_{17}F_2O_3K_2$ $[M+K]^+$ 313.0420, found 313.0435. mp 155 °C (decomposed).

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

An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxoundecanoate **3.1b-1** (1.6 g, 6.0 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (0.030 L) and DMF (0.17 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.50 mL, 5.8 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. Next, 3,5-dimethoxybenzyl alcohol (0.92 g, 5.5 mmol) was added dropwise at 0 °C followed by dropwise addition of Et_3N (1.5 mL, 11 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. H_2O (15 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 30 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (5% to 10%) for elution to furnish the compound **3.1b** as a colorless oil (1.5 g, 71%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.49 (d, *J* = 2.0 Hz, 2 H), 6.45 (t, *J* = 2.2 Hz, 1 H), 5.26 (s, 2 H), 3.80 (s, 6 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 1.63 (p, *J* = 7.0 Hz, 2 H), 1.32–1.23 (m, 10 H), 0.89 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.5 (t, *J* = 28.1 Hz), 161.5 (t, *J* = 31.2 Hz), 161.2, 136.1, 108.5 (t, *J* = 262.5 Hz), 106.2, 101.0, 68.9, 55.6, 36.8, 32.0, 29.4, 29.2, 29.0, 22.8, 22.6, 14.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –113.6 (s, 2 F). IR (film) 2953, 2930, 2856, 1780, 1747, 1599, 1464, 1431, 1379, 1346, 1302, 1207, 1155, 1068, 991, 947, 920, 837, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{29}F_2O_5$ $[M+H]^+$ 387.1983, found 387.1981.



3.2b

1-(3,5-dimethoxyphenyl)-2,2-difluoroundecan-3-one (3.2b)

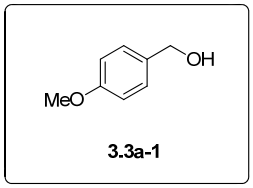
An oven-dried 20 mL scintillation vial was charged with substrate **3.1b** (193 mg, 0.500 mmol), $Pd(PPh_3)_4$ (20.2 mg, 0.0175 mmol), and a magnetic stir bar. Dry *o*-xylene (0.010 L) was added *via* a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 140 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). α,α,α-Trifluorotoluene (30 μL, 0.2443 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis. After determining the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. Removal of the solvents *in vacuo* and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.2b** as a colorless oil (95 mg, 55%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.39 (s, 3 H), 3.78 (s, 6 H), 3.24 (t, J = 16.8 Hz, 2 H), 2.48 (t, J = 7.2 Hz, 2 H), 1.56–1.48 (m, 2 H), 1.30–1.19 (m, 10 H), 0.89 (t, J = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1 (t, J = 30.6 Hz), 160.9, 133.3 (t, J = 4.4 Hz), 117.3 (t, J = 253.1 Hz), 108.8, 99.9, 55.5, 39.8 (t, J = 23.7 Hz), 37.4, 32.0, 29.4, 29.3, 29.0, 22.8, 22.6, 14.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –105.2 (t, J = 16.9 Hz, 2 F). IR (film) 2928, 2854, 1742, 1599, 1462, 1431, 1294, 1205, 1153, 1070, 835 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{28}F_2O_3Na$ $[M+Na]^+$ 365.1904, found 365.1920.

Experimental Procedures and Characterization of Compounds in Scheme 3.14

General Procedure A: An oven-dried one-neck round-bottom flask was charged with aldehyde (14 mmol). Methanol (30 mL) was added as solvent, followed by the addition of $NaBH_4$ (21 mmol) as solid portion. The reaction mixture was stirred at 0 °C for 30 min. H_2O was added to quench the reaction, and methanol was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) three times and the combined organic phases were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 30%) for elution to afford the desired benzyl alcohol.

General Procedure B: An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (7.2 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (35 mL) and DMF (0.19 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (6.9 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. Next, a solution of benzyl alcohol derivative (6.0 mmol) dissolved in dry CH_2Cl_2 (3.0 mL) was added dropwise at 0 °C, followed by dropwise addition of Et_3N (12 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. H_2O (10 mL) was added to quench the reaction, and the CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 25 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

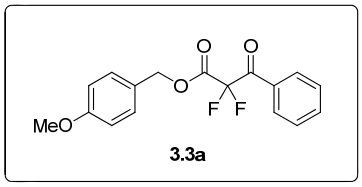
General Procedure C: An oven-dried 20 mL scintillation vial was charged with substrate **3.3a**–**h** (0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry *o*-xylene (0.010 L) was added *via* a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 120 °C, and stirred for 15 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). α,α,α-Trifluorotoluene (30 μL, 0.2443 mmol) or 2,2,2-trifluoroethanol (20 μL, 0.2745 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis. After determining the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. Removal of the solvents in *vacuo* and chromatographic purification provided the desired product **3.4a**–**h**.



3.3a-1

(4-methoxyphenyl)methanol (3.3a-1)

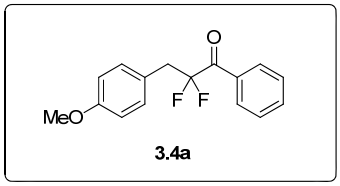
General procedure A was followed using *p*-anisaldehyde (3.6 mL, 30 mmol), $NaBH_4$ (1.7 g, 45 mmol), and MeOH (75 mL). Workup and chromatographic purification (20% to 30% EtOAc in hexanes) afforded the title compound **3.3a-1** as a colorless solid (4.1 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 4.61 (s, 2 H), 3.82 (s, 3 H), 1.77 (br, 1 H). Spectroscopic data matched that from the previous report.[5] mp 25–26 °C (lit.[6] 25 °C).



3.3a

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

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), **3.3a-1** (0.97 g, 7.0 mmol), Et_3N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH_2Cl_2 (45 mL). Workup and chromatographic purification (0% to 10% EtOAc in hexanes) afforded the title compound **3.3a** as a colorless oil (1.67 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 7.6 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.28 (s, 2 H), 3.81 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 26.9 Hz), 161.9 (t, *J* = 30.6 Hz), 160.3, 135.2, 131.1, 130.7, 130.1 (t, *J* = 2.5 Hz), 129.1, 126.0, 114.2, 109.9 (t, *J* = 263.1 Hz), 69.2, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.5 (s, 2 F). IR (film) 2945, 2908, 2835, 1770, 1699, 1597, 1502, 1464, 1450, 1290, 1250, 1159, 1124, 1034, 920, 987, 816, 771, 715, 685, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_4Na$ $[M+Na]^+$ 343.0758, found 343.0765.

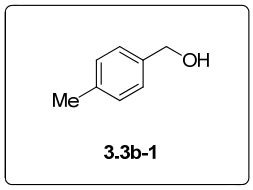


3.4a

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

General procedure C was followed using **3.3a** (160 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes)

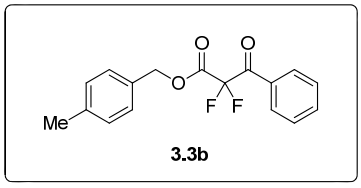
afforded the title compound **3.4a** as an off-white solid (116 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 3.80 (s, 3 H), 3.47 (t, *J* = 17.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.9 (t, *J* = 31.2 Hz), 159.3, 134.4, 132.4 (t, *J* = 1.9 Hz), 132.1, 130.3 (t, *J* = 3.1 Hz), 128.8, 123.3 (t, *J* = 3.7 Hz), 118.6 (t, *J* = 252.5 Hz), 114.1, 55.4, 39.6 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.9 (t, *J* = 16.9 Hz, 2 F). IR (film) 3003, 2935, 2837, 1699, 1612, 1599, 1514, 1448, 1279, 1252, 1178, 1115, 1034, 945, 903, 845, 822, 779, 714, 687, 663, 598 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2O_2Na$ $[M+Na]^+$ 299.0860, found 299.0847. mp 49–50 °C.



3.3b-1

***p*-tolylmethanol (3.3b-1)**

General procedure A was followed using *p*-tolualdehyde (3.5 mL, 30 mmol), $NaBH_4$ (1.7 g, 45 mmol), and MeOH (75 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound **3.3b-1** as an off-white solid (3.3 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 4.66 (d, *J* = 5.6 Hz, 2 H), 2.37 (s, 3 H), 1.66 (t, *J* = 5.8 Hz, 1 H). Spectroscopic data matched that from the previous report.[5] mp 57–58 °C (lit.[7] 59 °C).

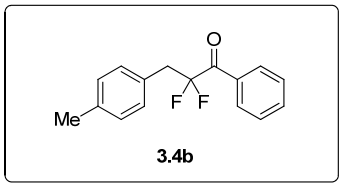


3.3b

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

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), **3.3b-1** (0.85 g, 7.0 mmol), Et_3N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH_2Cl_2 (45 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.3b** as a colorless oil (1.57 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ

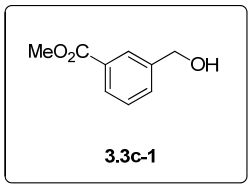
8.03 (d, *J* = 8.0 Hz, 2 H), 7.68–7.64 (m, 1 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 5.30 (s, 2 H), 2.35 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 139.1, 135.2, 131.2 (t, *J* = 1.9 Hz), 130.9, 130.1 (t, *J* = 2.5 Hz), 129.5, 129.1, 128.8, 110.0 (t, *J* = 263.7 Hz), 69.3, 21.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.5 (s, 2 F). IR (film) 3032, 2960, 1776, 1715, 1699, 1599, 1520, 1450, 1379, 1306, 1257, 1157, 1126, 1101, 1080, 922, 810, 754, 714, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3Na$ [M+Na]$^+$ 327.0809, found 327.0794.



3.4b

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

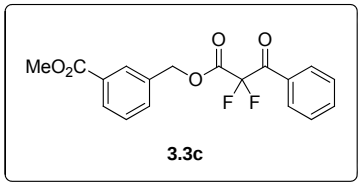
General procedure C was followed using **3.3b** (152 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.4b** as an off-white solid (110 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 7.6 Hz, 2 H), 3.49 (t, *J* = 17.8 Hz, 2 H), 2.34 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.8 (t, *J* = 31.2 Hz), 137.5, 134.4, 132.4 (t, *J* = 3.1 Hz), 130.9, 130.3 (t, *J* = 3.1 Hz), 129.4, 128.8, 128.3 (t, *J* = 3.7 Hz), 118.6 (t, *J* = 252.5 Hz), 40.0 (t, *J* = 23.1 Hz), 21.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.8 (t, *J* = 18.8 Hz, 2 F). IR (film) 3028, 2924, 1703, 1599, 1516, 1448, 1279, 1171, 1115, 1040, 937, 903, 769, 714, 687, 663, 600 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2ONa$ [M+Na]$^+$ 283.0910, found 283.0901. mp 67–68 °C.



3.3c-1

methyl 3-(hydroxymethyl)benzoate (3.3c-1)

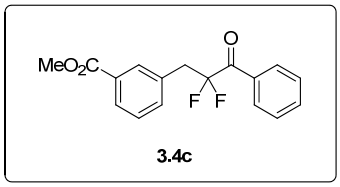
The preparation was followed according to literature report[8] using 3-(methoxycarbonyl)benzoic acid (1.8 g, 0.010 mol), $BH_3.SMe_2$ (0.020 L, 0.020 mol), and THF (20 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound **3.3c-1** as a colorless liquid (1.55 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (t, *J* = 1.6 Hz, 1 H), 7.97 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 4.76 (s, 2 H), 3.93 (s, 3 H), 1.91 (br, 1 H). HRMS (ESI, *m/z*): calcd for $C_9H_{11}O_3$ $[M+H]^+$ 167.0708, found 167.0705. Spectroscopic data matched that from the previous report.[8]



3.3c

methyl 3-(((2,2-difluoro-3-oxo-3-phenylpropanoyl)oxy)methyl)benzoate (3.3c)

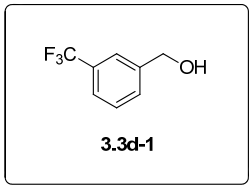
General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (1.4 g, 6.0 mmol), oxalyl chloride (0.46 mL, 5.5 mmol), **3.3c-1** (0.83 g, 5.0 mmol), Et_3N (1.4 mL, 0.010 mol), DMF (0.15 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.3c** as a colorless oil (1.17 g, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05–7.99 (m, 4 H), 7.66 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.53–7.46 (m, 3 H), 7.43 (td, *J* = 7.6, 0.4 Hz, 1 H), 5.38 (s, 2 H), 3.93 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 26.9 Hz), 166.6, 161.8 (t, *J* = 31.2 Hz), 135.4, 134.3, 133.0, 131.0, 130.9, 130.3, 130.1 (t, *J* =2.5 Hz), 129.8, 129.2, 129.1, 110.0 (t, *J* = 263.7 Hz), 68.5, 52.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F). IR (film) 2955, 1778, 1722, 1597, 1450, 1435, 1308, 1290, 1207, 1159, 1103, 922, 750, 712, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{14}F_2O_5Na$ $[M+Na]^+$ 371.0707, found 371.0706.



3.4c

methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)benzoate (3.4c)

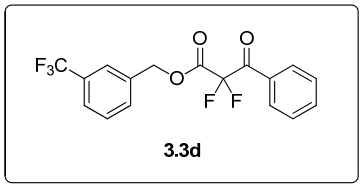
General procedure C was followed using **3.3c** (174 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.4c** as an off-white solid (123 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, *J* = 8.8, 1.6 Hz, 2 H), 8.02 (s, 1 H), 7.99 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.65–7.61 (m, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 3.93 (s, 3 H), 3.58 (t, *J* = 17.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (t, *J* = 30.6 Hz), 167.0, 135.6, 134.6, 132.2, 132.1 (t, *J* = 2.5 Hz), 132.0 (t, *J* = 3.1 Hz), 130.6, 130.4 (t, *J* = 3.1 Hz), 129.1, 128.9, 128.7, 118.3 (t, *J* = 253.1 Hz), 52.4, 39.9 (t, *J* = 22.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.6 (t, *J* = 16.9 Hz, 2 F). IR (film) 3065, 2953, 1724, 1703, 1597, 1448, 1435, 1288, 1203, 1173, 1111, 1086, 1040, 908, 741, 715, 694, 665, 604 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3Na$ $[M+Na]^+$ 327.0809, found 327.0800. mp 44–45 °C.



3.3d-1

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

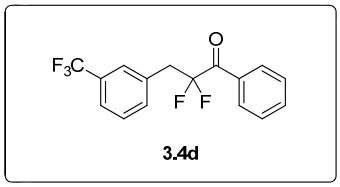
General procedure A was followed using 3-(trifluoromethyl)benzaldehyde (1.3 mL, 10 mmol), $NaBH_4$ (0.57 g, 15 mmol), and MeOH (25 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound **3.3d-1** as a colorless oil (1.73 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 1 H), 7.57–7.55 (m, 2 H), 7.49 (dd, *J* = 8.4, 6.8 Hz, 1 H), 4.78 (d, *J* = 5.6 Hz, 2 H), 1.83–1.79 (m, 1 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –62.6 (s, 3 F). HRMS (ESI, *m/z*): calcd for $C_8H_6F_3O$ $[M-H]^+$ 175.0371, found 175.0372. Spectroscopic data matched that from the previous report.[9]



3.3d

3-(trifluoromethyl)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3d)

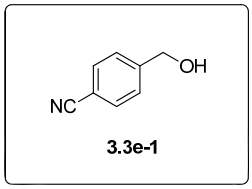
General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), **3.3d-1** (1.2 g, 7.0 mmol), Et_3N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH_2Cl_2 (45 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **3.3d** as a colorless oil (1.58 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 8.0 Hz, 2 H), 7.70–7.65 (m, 1 H), 7.61 (d, *J* = 7.2 Hz, 1 H), 7.57 (s, 1 H), 7.53–7.46 (m, 4 H), 5.40 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.8 (t, *J* = 30.6 Hz), 135.5, 134.9, 131.8, 131.4 (q, *J* = 32.5 Hz), 131.0 (t, *J* = 2.5 Hz), 130.1 (t, *J* = 2.5 Hz), 129.5, 129.2, 125.9 (q, *J* = 3.7 Hz), 125.3 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 271.2 Hz), 110.1 (t, *J* = 264.4 Hz), 68.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F), –62.7 (s, 3 F). IR (film) 3070, 1780, 1715, 1701, 1599, 1450, 1333, 1310, 1205, 1165, 1128, 1099, 1074, 920, 885, 802, 700, 685, 661, 588 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{12}F_5O_3$ $[M+H]^+$ 359.0707, found 359.0704.



3.4d

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

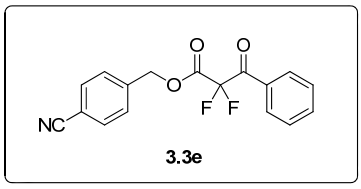
General procedure C was followed using **3.3d** (179 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), and *o*-xylene (0.010 L). The reaction was run at 140 °C. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.4d** as an off-white solid (95.0 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.60–7.44 (m, 6 H), 3.59 (t, *J* = 17.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.1 (t, *J* = 30.6 Hz), 134.7, 134.5, 132.6 (t, *J* = 3.7 Hz), 132.0 (t, *J* = 3.1 Hz), 131.0 (q, *J* = 32.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.1, 128.9, 127.8 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 3.4 Hz), 124.2 (q, *J* = 270.9 Hz), 118.2 (t, *J* = 253.7 Hz), 39.9 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.5 (t, *J* = 16.9 Hz, 2 F), –62.7 (s, 3 F). IR (film) 3068, 2928, 1699, 1599, 1450, 1329, 1279, 1169, 1126, 1076, 1040, 920, 771, 715, 702, 658 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_5O$ $[M+H]^+$ 315.0808, found 315.0794. mp 49–50 °C.



3.3e-1

4-(hydroxymethyl)benzonitrile (3.3e-1)

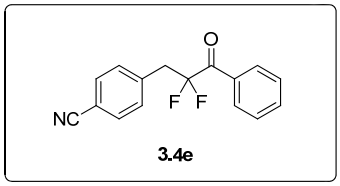
General procedure A was followed using 4-cyanobenzaldehyde (3.0 g, 23 mmol), $NaBH_4$ (1.3 g, 34 mmol), and MeOH (60 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound **3.3e-1** as an off-white solid (2.8 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, *J* = 8.0 Hz, 2 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 4.79 (d, *J* = 3.6 Hz, 2 H), 2.05–2.01 (m, 1 H). Spectroscopic data matched that from the previous report.[10a] mp 41–42 °C (lit.[10b] 41–42 °C).



3.3e

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

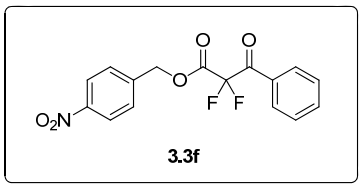
General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), **3.3e-1** (0.93 g, 7.0 mmol), Et_3N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH_2Cl_2 (45 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound **3.3e** as a pale yellow solid (1.3 g, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.0 Hz, 2 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 5.40 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.7 (t, *J* = 30.6 Hz), 139.1, 135.6, 132.7, 130.9 (t, *J* = 2.5 Hz), 130.1 (t, *J* = 2.5 Hz), 129.3, 128.7, 118.5, 112.9, 110.1 (t, *J* = 264.4 Hz), 67.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.0 (s, 2 F). IR (film) 3068, 2231, 1778, 1715, 1699, 1597, 1450, 1308, 1159, 1099, 926, 823, 714, 685, 669 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{12}F_2NO_3$ $[M+H]^+$ 316.0785, found 316.0778. mp 79–80 °C.



3.4e

4-(2,2-difluoro-3-oxo-3-phenylpropyl)benzonitrile (3.4e)

General procedure C was followed using **3.3e** (157.6 mg, 0.500 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol), and *o*-xylene (0.050 L) in 100 mL Schlenk tube. The reaction was run at 140 °C for 24 h. Workup and chromatographic purification (20% to 50% CH_2Cl_2 in hexanes) afforded the title compound **3.4e** as a pale yellow solid (44.0 mg, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 2 H), 7.67–7.62 (m, 3 H), 7.52–7.45 (m, 4 H), 3.59 (t, *J* = 17.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.7 (t, *J* = 31.2 Hz), 137.2 (t, *J* = 3.7 Hz), 134.8, 132.3, 131.9, 131.7 (t, *J* = 2.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.0, 118.8, 118.1 (t, *J* = 254.4 Hz), 111.9, 40.1 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.9 (t, *J* = 18.8 Hz, 2 F). IR (film) 3068, 2926, 2230, 1703, 1597, 1506, 1448, 1279, 1209, 1171, 1115, 1038, 943, 904, 777, 714, 656, 602, 552 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_2NO$ $[M+H]^+$ 272.0887, found 272.0875. mp 79 °C.

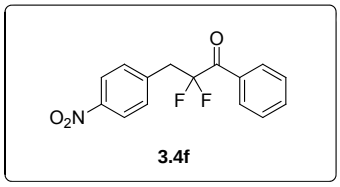


3.3f

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

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 4-nitrobenzyl alcohol (0.92 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH_2Cl_2 (35 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound **3.3f** as an off-white solid (1.03 g, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, *J* = 8.4 Hz, 2 H), 8.07 (dd, *J* = 8.6, 1.4 Hz, 2 H), 7.70 (tt, *J* = 7.4, 1.5 Hz, 1 H), 7.54–7.48 (m, 4 H), 5.45 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.7 (t, *J* = 30.6 Hz), 148.2, 141.0, 135.6, 130.9, 130.2 (t, *J* = 2.5 Hz), 129.3, 128.8, 124.1, 110.2 (t, *J* = 265.0 Hz), 67.4. ^{19}F

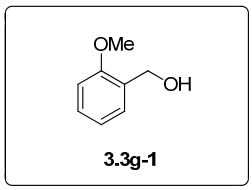
NMR ($CDCl_3$, 376 MHz) δ –107.0 (s, 2 F). IR (film) 3080, 1778, 1715, 1699, 1599, 1526, 1450, 1348, 1310, 1257, 1159, 1128, 1101, 926, 843, 791, 739, 714, 687 cm^1. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_2NO_5$ $[M+H]^+$ 336.0684, found 336.0683. mp 53–54 °C.



3.4f

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

General procedure C was followed using **3.3f** (167.6 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), and *o*-xylene (0.010 L). The reaction was run at 140 °C for 24 h. Workup and chromatographic purification (20% to 50% CH_2Cl_2 in hexanes) afforded the title compound **3.4f** as an off-white solid (34.2 mg, 23%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, *J* = 8.0 Hz, 2 H), 8.08 (d, *J* = 8.0 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.54–7.48 (m, 4 H), 3.64 (t, *J* = 17.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.7 (t, *J* = 30.6 Hz), 147.7, 139.2 (t, *J* = 3.1 Hz), 134.9, 132.1, 131.7 (t, *J* = 2.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.0, 123.7, 118.1 (t, *J* = 254.4 Hz), 39.8 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.8 (t, *J* = 16.9 Hz, 2 F). IR (film) 3080, 2928, 1699, 1599, 1520, 1450, 1348, 1279, 1171, 1115, 1055, 1040, 904, 856, 773, 733, 715, 694, 669, 600 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{12}F_2NO_3$ $[M+H]^+$ 292.0785, found 292.0786. mp 89–90 °C.

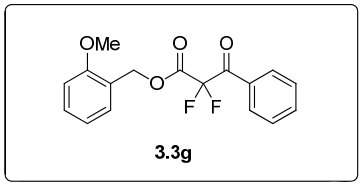


3.3g-1

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

General procedure A was followed using *o*-anisaldehyde (2.7 g, 20 mmol), $NaBH_4$ (1.1 g, 30 mmol), and MeOH (50 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound **3.3g-1** as a colorless oil (2.3 g, 83%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.28 (m, 2 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.70 (d, *J* = 6.0 Hz, 2 H), 3.88 (s, 3 H), 2.32 (t, *J* = 6.4

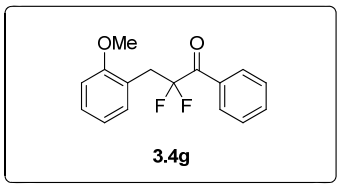
Hz, 1 H). HRMS (ESI, *m/z*): calcd for $C_8H_9O_2$ $[M–H]^+$ 137.0603, found 137.0587. Spectroscopic data matched that from the previous report.[11]



3.3g

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

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), **3.3g-1** (0.83 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH_2Cl_2 (35 mL). Workup and chromatographic purification (2% to 10% EtOAc in hexanes) afforded the title compound **3.3g** as a colorless oil (1.51 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 8.0 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 7.4 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 5.40 (s, 2 H), 3.73 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 157.8, 135.2, 131.3, 130.6, 130.3, 130.1 (t, *J* = 2.5 Hz), 129.1, 122.2, 120.6, 110.6, 109.9 (t, *J* =263.1 Hz), 65.1, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.6 (s, 2 F). IR (film) 3070, 2964, 2841, 1770, 1715, 1699, 1599, 1497, 1466, 1450, 1381, 1308, 1254, 1157, 1124, 1101, 1028, 922, 808, 756, 712, 687, 586 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_4Na$ $[M+Na]^+$ 343.0758, found 343.0746.

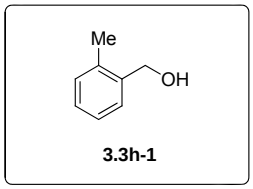


3.4g

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

General procedure C was followed using **3.3g** (160 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.4g** as a colorless oil (124 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 7.6 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.32–7.29 (m, 1 H), 7.28–7.25 (m, 1

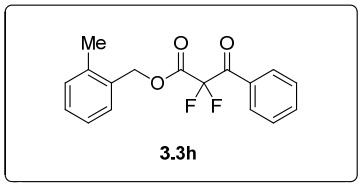
H), 6.95 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 3.60 (t, *J* = 17.4 Hz, 2 H), 3.58 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.7 (t, *J* = 29.4 Hz), 158.1, 134.1, 132.6, 132.5, 130.2 (t, *J* = 3.7 Hz), 129.4, 128.6, 120.7, 120.0 (t, *J* = 4.4 Hz), 118.8 (t, *J* = 251.9 Hz), 110.6, 55.1, 35.2 (t, *J* = 23.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.8 (t, *J* = 18.8 Hz, 2 F). IR (film) 2939, 2839, 1703, 1599, 1497, 1464, 1450, 1290, 1252, 1176, 1124, 1051, 1026, 933, 754, 714, 687, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2O_2Na$ $[M+Na]^+$ 299.0860, found 299.0847.



3.3h-1

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

General procedure A was followed using *o*-tolualdehyde (1.7 g, 15 mmol), $NaBH_4$ (0.87 g, 23 mmol), and MeOH (38 mL). Workup and chromatographic purification (15% to 35% EtOAc in hexanes) afforded the title compound **3.3h-1** as a colorless solid (1.73 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.36 (m, 1 H), 7.24–7.18 (m, 3 H), 4.71 (d, *J* = 2.8 Hz, 2 H), 2.38 (s, 3 H), 1.58 (br, 1 H). Spectroscopic data matched that from the previous report.[5] mp 35–36 °C (lit.[5] 37–38 °C).

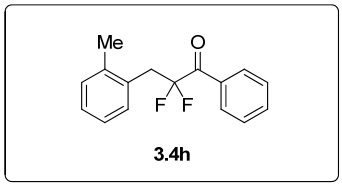


3.3h

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

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate **3.1a-1** (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), **3.3h-1** (0.73 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH_2Cl_2 (35 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.3h** as a colorless oil (1.48 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 7.6 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.30–7.25 (m, 2 H), 7.18 (t, *J* = 6.8 Hz, 2 H), 5.36 (s, 2 H), 2.28 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.9 (t,

J = 30.6 Hz), 137.6, 135.3, 131.9, 131.1, 130.7, 130.1 (t, *J* = 2.5 Hz), 129.5, 129.1, 126.3, 110.0 (t, *J* = 263.1 Hz), 67.9, 18.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F). IR (film) 3068, 2974, 1776, 1715, 1697, 1599, 1450, 1310, 1257, 1157, 1101, 1078, 922, 804, 762, 744, 712, 685, 584 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3Na$ $[M+Na]^+$ 327.0809, found 327.0801.

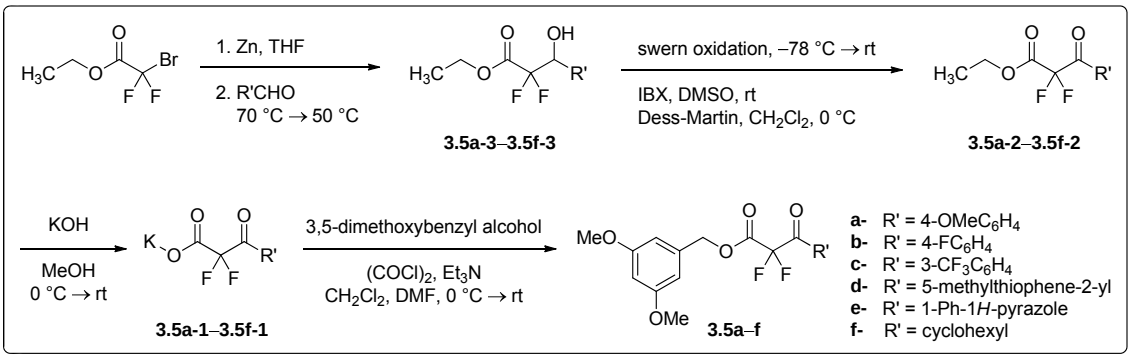


3.4h

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

General procedure C was followed using **3.3h** (152 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.4h** as a colorless oil (114 mg, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.28–7.26 (m, 1 H), 7.22–7.15 (m, 3 H), 3.56 (t, *J* = 18.4 Hz, 2 H), 2.37 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0 (t, *J* = 31.2 Hz), 138.3, 134.5, 132.3, 131.9, 130.8, 130.4 (t, *J* = 3.1 Hz), 130.0 (t, *J*= 2.5 Hz), 128.8, 128.0, 126.1, 119.1 (t, *J* = 252.5 Hz), 36.9 (t, *J* = 23.1 Hz), 20.2 (t, *J* = 1.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.6 (t, *J* = 18.8 Hz, 2 F). IR (film) 3063, 3024, 1703, 1597, 1497, 1448, 1275, 1184, 1171, 1115, 1057, 1028, 904, 744, 714, 687, 665, 602 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2ONa$ $[M+Na]^+$ 283.0910, found 283.0905.

Experimental Procedures and Characterization of Compounds in Scheme 3.16

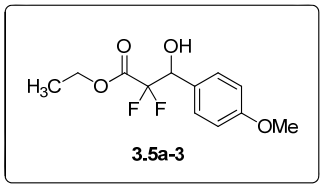


General Procedure D: An oven-dried three-neck flask was charged with activated Zn (3.2 g, 49 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with $N_{2(g)}$ three times. Dry THF (0.050 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.25 mL, 2.9 mmol) under $N_{2(g)}$. To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of aldehyde (25 mmol) and ethyl bromodifluoroacetate (25 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to 0 °C, and 1 N $HCl_{(aq)}$ was added until the residual Zn was consumed (roughly 100 mL). The reaction mixture was warmed to rt, and transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

General Procedure E: An oven-dried three-neck flask was equipped with a liquid addition funnel, three-way valve and two rubber septa, evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (0.10 L) and oxalyl chloride (59 mmol) were added sequentially at rt, and the reaction solution was cooled to –78 °C. A solution of anhydrous DMSO (78 mmol) in dry CH_2Cl_2 (0.010 L) was added dropwise at –78 °C, and then the reaction solution was stirred continually at this temperature for 1 h. Next, a solution of alcohol (19.5 mmol) dissolved in dry CH_2Cl_2 (0.010 L) was added dropwise at –78 °C, and then the resulting reaction solution was stirred at this temperature for 1 h. Et_3N (117 mmol) was added dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was gradually warmed to rt, and stirred at rt for 2 h. H_2O (0100 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

General Procedure F: A one-neck round-bottom flask was charged with β-keto ester (16 mmol), and MeOH (8.0 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (16 mmol) dissolved in MeOH (8.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred at rt for 7 h. MeOH was removed under reduced pressure. EtOAc (8.0 mL) and ether (8.0 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried *in vacuo* to give potassium salt.

General Procedure G: An oven-dried one-neck round-bottom flask was charged with potassium salt (5.0 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (15 mL) and DMF (0.75 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (5.0 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol (6.5 mmol) dissolved in dry CH_2Cl_2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et_3N (6.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H_2O (8.0 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

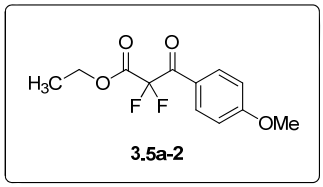


3.5a-3

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

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), *p*-anisaldehyde (3.0 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.5a-3** as a colorless oil (5.4 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 5.12 (ddd, J = 15.2, 8.0, 5.2 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 3.82 (s, 3 H),

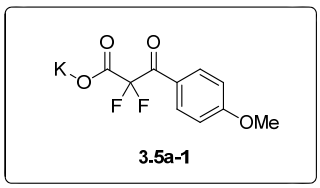
2.63 (d, *J* = 5.2 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (t, *J* = 31.2 Hz), 160.5, 129.2, 126.7, 114.1, 114.0 (dd, *J* = 257.5, 252.5 Hz), 73.6 (dd, *J* = 26.2, 23.8 Hz), 63.3, 55.5, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.4 (dd, *J* = 259.4, 15.0 Hz, 1 F), –114.2 (dd, *J* = 259.4, 7.5 Hz, 1 F). HRMS (ESI, *m/z*): calcd for $C_{12}H_{14}F_2O_4Na$ $[M+Na]^+$ 283.0758, found 283.0746. Spectroscopic data matched that from the previous report.[12]



3.5a-2

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

General procedure E was followed using oxalyl chloride (5.0 mL, 59 mmol), DMSO (5.5 mL, 78 mmol), **3.5a-3** (5.07 g, 19.5 mmol), Et_3N (16 mL, 120 mmol) and CH_2Cl_2 (120 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.5a-2** as a colorless oil (4.38 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.8 Hz, 2 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 3.91 (s, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F). HRMS (ESI, *m/z*): calcd for $C_{12}H_{12}F_2O_4Na$ $[M+Na]^+$ 281.0601, found 281.0587. Spectroscopic data matched that from the previous report.[13]

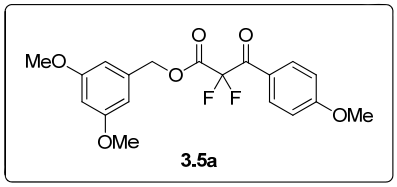


3.5a-1

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

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

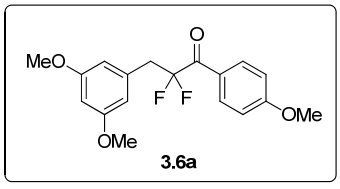
1605, 1516, 1383, 1325, 1277, 1180, 1151, 1128, 1028, 922, 847, 816, 717, 613, 584 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_7F_2K_2O_4$ $[M+K]^+$ 306.9587, found 306.9574. mp 150–151 °C.



3.5a

3,5-dimethoxybenzyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (3.5a)

General procedure G was followed using potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate **3.5a-1** (1.6 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.7 mmol), 3,5-dimethoxybenzyl alcohol (0.84 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), DMF (0.19 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound **3.5a** as an off-white solid (1.5 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 8.8 Hz, 2 H), 6.94 (dt, *J* = 9.2, 2.4 Hz, 2 H), 6.45 (d, *J* = 2.4 Hz, 2 H), 6.41 (t, *J* = 2.2 Hz, 1 H), 5.28 (s, 2 H), 3.90 (s, 3 H), 3.76 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 183.7 (t, *J* = 27.5 Hz), 165.3, 162.1 (t, *J* = 30.6 Hz), 161.1, 136.2, 132.7 (t, *J* = 2.5 Hz), 124.0 (t, *J* = 2.5 Hz), 114.5, 110.3 (t, *J* = 263.1 Hz), 106.1, 101.0, 68.9, 55.8, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.0 (s, 2 F). IR (film) 2957, 2937, 2841, 1774, 1701, 1686, 1599, 1512, 1458, 1431, 1311, 1267, 1157, 1099, 1067, 1024, 922, 843, 791, 768, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{18}F_2O_6Na$ $[M+Na]^+$ 403.0969, found 403.0960. mp 52–53 °C.

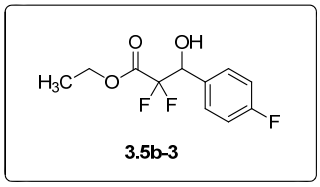


3.6a

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

General procedure C was followed using **3.5a** (190 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.6a** as a colorless oil (128 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 6.46 (s, 2 H), 6.40 (t, *J* = 2.2 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 6

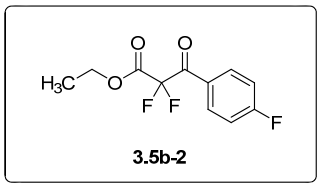
H), 3.44 (t, J = 17.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.0 (t, J = 30.0 Hz), 164.6, 160.8, 133.7 (t, J = 3.7 Hz), 132.9 (t, J = 3.1 Hz), 125.2 (t, J = 1.9 Hz), 118.7 (t, J = 253.7 Hz), 114.1, 109.1, 99.8, 55.7, 55.5, 40.7 (t, J = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.1 (t, J = 18.8 Hz, 2 F). IR (film) 3003, 2957, 2939, 2841, 1691, 1599, 1578, 1512, 1460, 1431, 1317, 1265, 1205, 1165, 1151, 1113, 1068, 1030, 947, 879, 843, 796, 769, 715, 696, 688, 594 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{18}F_2O_4Na$ $[M+Na]^+$ 359.1071, found 359.1056.



3.5b-3

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

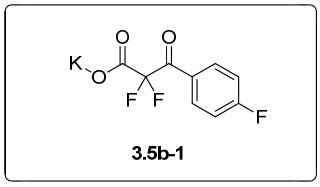
General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), 4-fluorobenzaldehyde (2.6 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.5b-3** as a colorless oil (5.1 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.42 (m, 2 H), 7.10 (t, J = 8.8 Hz, 2 H), 5.18 (ddd, J = 15.2, 8.0, 5.2 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 2.71 (d, J = 4.8 Hz, 1 H), 1.32 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7 (t, J = 31.2 Hz), 163.4 (d, J = 246.2 Hz), 130.4 (t, J = 2.5 Hz), 129.8 (d, J = 7.5 Hz), 115.6 (d, J = 21.2 Hz), 113.7 (dd, J = 257.5, 252.5 Hz), 73.3 (dd, J = 27.5, 23.8 Hz), 63.5, 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.6 (dd, J = 263.2, 15.0 Hz, 1 F), –113.8 (dd, J = 263.2, 7.5 Hz, 1 F), –112.2 (m, 1 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_{11}F_3O_3Li$ $[M+Li]^+$ 255.0820, found 255.0831. Spectroscopic data matched that from the previous report.[12]



3.5b-2

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

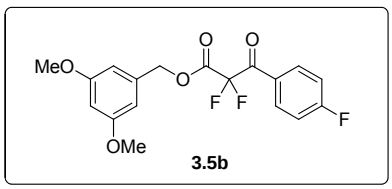
General procedure E was followed using oxalyl chloride (5.0 mL, 58 mmol), DMSO (5.5 mL, 77 mmol), **3.5b-3** (4.76 g, 19.2 mmol), Et_3N (16 mL, 120 mmol) and CH_2Cl_2 (130 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.5b-2** as a colorless oil (3.93 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16–8.13 (m, 2 H), 7.21 (t, *J* = 8.6 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.2 (t, *J* = 28.1 Hz), 167.1 (d, *J* = 257.5 Hz), 161.9 (t, *J* = 30.0 Hz), 133.2 (dt, *J* = 8.8, 3.1 Hz), 127.6 (m), 116.6 (d, *J* = 22.5 Hz), 110.0 (t, *J* = 262.5 Hz), 64.1, 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.5 (s, 2 F), –100.4 (m, 1 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_9F_3O_3Na$ $[M+Na]^+$ 269.0401, found 269.0411. Spectroscopic data matched that from the previous report.[14]



3.5b-1

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

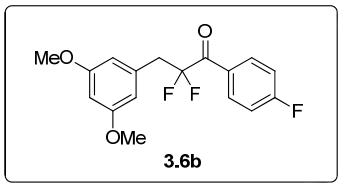
General procedure F was followed using **3.5b-2** (3.72 g, 15.1 mmol), KOH (0.850 g, 15.1 mmol), and MeOH (0.030 L). Workup afforded the title compound **3.5b-1** as a colorless solid (3.28 g, 85%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.09 (dd, *J* = 8.6, 5.4 Hz, 2 H), 7.37 (t, *J* = 9.0 Hz, 2 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 188.4 (t, *J* = 28.1 Hz), 165.3 (d, *J* = 252.5 Hz), 162.2 (t, *J* = 23.8 Hz), 132.3 (d, *J* = 10.0 Hz), 129.3 (d, *J* = 3.8 Hz), 115.8 (d, *J* = 21.2 Hz), 111.3 (t, *J* = 261.2 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –105.4 (s, 2 F), –104.5 (m, 1 F). IR (film) 3086, 1718, 1678, 1645, 1605, 1512, 1404, 1300, 1250, 1161, 1099, 912, 849, 816, 764, 717, 688, 573, 521, 480 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_9H_4F_3K_2O_3$ $[M+K]^+$ 294.9387, found 294.9375. mp 173–174 °C decomposed.



3.5b

3,5-dimethoxybenzyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (3.5b)

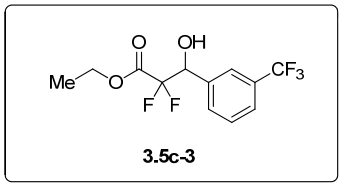
General procedure G was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate **3.5b-1** (1.5 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.7 mmol), 3,5-dimethoxybenzyl alcohol (0.84 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), DMF (0.19 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (5% to 15% EtOAc in hexanes) afforded the title compound **3.5b** as a light yellow oil (1.3 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11–8.07 (m, 2 H), 7.16 (t, *J* = 8.6 Hz, 2 H), 6.44–6.42 (m, 3 H), 5.28 (s, 2 H), 3.77 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.0 (t, *J* = 27.5 Hz), 167.0 (d, *J* = 257.5 Hz), 161.7 (t, *J* = 30.6 Hz), 161.1, 136.0, 133.1 (dt, *J* = 10.0, 2.5 Hz), 127.5 (d, *J* = 2.5 Hz), 116.6 (d, *J* = 21.2 Hz), 110.0 (t, *J* = 263.7 Hz), 106.3, 100.9, 69.1, 55.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –100.4 (m, 1 F), –107.3 (s, 2 F). IR (film) 2959, 2941, 2841, 1774, 1701, 1599, 1508, 1473, 1431, 1304, 1244, 1207, 1159, 1101, 1068, 922, 850, 834, 766, 715, 690, 615, 575 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{15}F_3O_5Na$ $[M+Na]^+$ 391.0769, found 391.0762.



3.6b

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

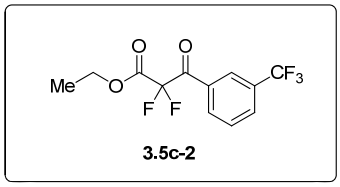
General procedure C was followed using **3.5b** (184 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.6b** as a colorless oil (133 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11–8.07 (m, 2 H), 7.15 (t, *J* = 8.8 Hz, 2 H), 6.45 (d, *J* = 2.4 Hz, 2 H), 6.40 (t, *J* = 2.2 Hz, 1 H), 3.77 (s, 6 H), 3.45 (t, *J* = 17.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.1 (t, *J* = 31.2 Hz), 166.5 (d, *J* = 256.2 Hz), 160.8, 133.4 (t, *J* = 3.7 Hz), 133.3 (dt, *J* = 10.0, 3.7 Hz), 128.7 (q, *J* = 2.5 Hz), 118.5 (t, *J* = 253.1 Hz), 116.1 (d, *J* = 22.5 Hz), 109.1, 99.8, 55.5, 40.4 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.3 (m, 1 F), –98.1 (t, *J* = 16.9 Hz, 2 F). IR (film) 3001, 2939, 2839, 1701, 1599, 1508, 1466, 1458, 1431, 1412, 1319, 1277, 1242, 1205, 1161, 1111, 1070, 947, 879, 849, 771, 712, 688, 613, 596, 586 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{16}F_3O_3$ $[M+H]^+$ 325.1052, found 325.1061.



3.5c-3

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

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), 3-(trifluoromethyl)benzaldehyde (3.3 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.5c-3** as a colorless oil (5.7 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (s, 1 H), 7.66 (d, *J* = 7.6 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 5.29–5.23 (m, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 2.95 (d, *J* = 4.8 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5 (t, *J* = 31.2 Hz), 135.7, 131.3, 131.0 (q, *J* = 32.1 Hz), 129.1, 126.2 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 4.1 Hz), 124.1 (q, *J* = 270.9 Hz), 113.6 (dd, *J* = 258.7 Hz, 253.7 Hz), 73.3 (dd, *J* = 28.1 Hz, 24.4 Hz), 63.6, 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.3 (dd, *J* = 263.2, 15.0 Hz, 1 F), –113.0 (dd, *J* = 263.2, 7.5 Hz, 1 F), –62.7 (s, 3 F). IR (film) 3493, 2989, 2945, 1759, 1452, 1377, 1331, 1169, 1128, 1074, 854, 783, 729, 702, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{11}F_5O_3Na$ $[M+Na]^+$ 321.0526, found 321.0533.

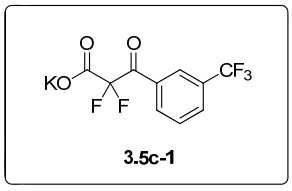


3.5c-2

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

Dess-Martin periodinane (8.53 g, 20.1 mmol) was added into a solution of compound **3.5c-3** (4.61 g, 15.5 mmol) dissolved in CH_2Cl_2 (0.120 L) at 0 °C, and the solution was stirred at rt for 3 h. CH_2Cl_2 was removed under reduced pressure, and the residue was charged with ether (170 mL). Next, the mixture was cooled to 0 °C, and $Na_2S_2O_3$ (sat'd), water and $NaHCO_3$ (sat'd, 75 mL each) were added into the mixture and stirred until the two phases were generated. The solution was transferred to a separation funnel, and the organic layer was collected. The aqueous layer was extracted with ether (2 x 170 mL), and the

combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the title compound **3.5c-2** as a colorless liquid (4.5g, 98%). Occasionally, a small amount of the hydrate form of the ketone was observed by ^{19}F NMR [($CDCl_3$, 376 MHz) δ –117.2 (s, 2 F)]. To convert the hydrate form to keto form, the crude product was stirred together with activated 4Å molecular sieves in dry toluene for several hours. The molecular sieves were removed by filtration and washed with dry toluene. The filtrate was concentrated, and the product was dried *in vacuo*. The colorless liquid product was used in the next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (s, 1 H), 8.28 (d, J = 7.6 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.70 (t, J = 7.8 Hz, 1 H), 4.42 (q, J = 7.2 Hz, 2 H), 1.35 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.8 (t, J = 28.1 Hz), 161.5 (t, J = 30.6 Hz), 133.3 (t, J = 2.5 Hz), 132.1, 131.8 (t, J = 1.9 Hz), 131.6 (q, J = 3.3 Hz), 127.0 (q, J = 3.2 Hz), 123.5 (q, J = 270.9 Hz), 109.8 (t, J = 263.1 Hz), 64.3, 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.7 (s, 2 F), –63.1 (s, 3 F). IR (film) 2989, 1778, 1713, 1614, 1375, 1337, 1269, 1161, 1134, 1076, 1009, 941, 785, 692, 651 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{10}F_5O_3$ $[M+H]^+$ 297.0550, found 297.0538.

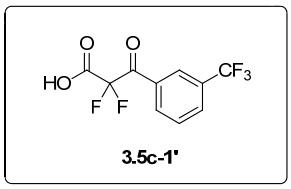


3.5c-1

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

A one-neck round-bottom flask was charged with **3.5c-2** (4.80 g, 16.2 mmol), and MeOH (35 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.910 g, 16.2 mmol) dissolved in MeOH (20 mL) was added dropwise, and then the reaction solution was warmed to rt. The reaction mixture was stirred at rt for 12 h, after which the solvent was removed under reduced pressure. Ether (20 mL) and hexanes (5 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried *in vacuo* to give the compound **3.5c-1** as an off-white solid (4.1 g, 83%). ^1H NMR (DMSO-d_6, 400 MHz) δ 8.30 (s, 1 H), 8.28 (d, J = 8.0 Hz,1 H), 8.05 (d, J = 7.6 Hz, 1 H), 7.80 (t, J = 8.0 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 189.1 (t, J

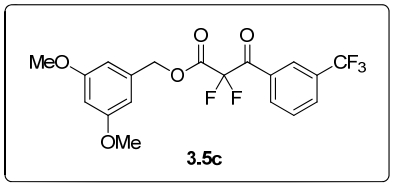
= 28.1 Hz), 162.8 (t, *J* = 23.7 Hz), 133.4, 133.2, 130.3, 130.2, 129.6 (q, *J* = 32.1 Hz), 125.7, 123.8 (q, *J* = 270.9 Hz) 111.4 (t, *J* = 261.9 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –105.7 (s, 2 F), –61.5 (s, 3 F). IR (film) 1701, 1670, 1389, 1333, 1269, 1128, 1074, 920, 814, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_5F_5KO_3$ $[M+H]^+$ 306.9796, found 306.9783. mp 145 °C decomposed.



3.5c-1'

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

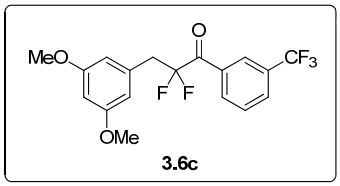
A one-neck round-bottom flask was charged with **3.5c-1** (1.4 g, 4.6 mmol), and $CHCl_3$ (25 mL) was added at rt. The resulting suspension was cooled to 0 °C, and then a pre-cooled solution of HCl in 1,4-dioxane (4 N, 1.5 mL) was added dropwise. The mixture solution was stirred at 0 °C until the thick white suspension disappeared, leaving a translucent turbid suspension of KCl. Then, the mixture was filtered through a pad of anhydrous Na_2SO_4, and the solid portion was washed with $CHCl_3$. The filtrate was concentrated under reduced pressure, and the residue was dried *in vacuo* to give the compound **3.5c-1'** as a slightly pink solid (1.2 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (s, 1 H), 8.31 (d, *J* = 7.6 Hz, 1 H), 7.97 (d, *J* = 7.6 Hz, 1 H), 7.72 (t, *J* = 7.8 Hz, 1 H), 6.80 (br, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.7 (t, *J* = 28.7 Hz), 165.0 (t, *J* = 30.6 Hz), 133.4, 132.1 (q, *J* = 33.4 Hz), 132.0 (t, *J* = 3.7 Hz), 131.4, 130.1, 127.1 (q, *J* = 3.4 Hz), 123.4 (q, *J* = 270.9 Hz), 110.0 (t, *J* = 264.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.6 (s, 2 F), –63.1 (s, 3 F). IR (film) 3088, 1769, 1709, 1612, 1439, 1335, 1271, 1167, 1130, 1074, 935, 916, 818, 793, 758, 690 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_6F_5O_3$ $[M+H]^+$ 269.0237, found 269.0242. mp 81–82 °C.



3.5c

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

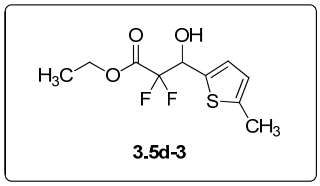
General procedure G was followed using **3.5c-1'** (1.1 g, 4.3 mmol), oxalyl chloride (0.35 mL, 4.1 mmol), 3,5-dimethoxybenzyl alcohol (0.69 g, 4.1 mmol), Et_3N (1.1 mL, 8.2 mmol), DMF (0.12 mL), and CH_2Cl_2 (25 mL). Workup and chromatographic purification (30% to 60% CH_2Cl_2 in hexanes) afforded the title compound **3.5c** as a light yellow oil (1.2 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 6.45–6.42 (m, 3 H), 5.29 (s, 2 H), 3.77 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.6 (t, *J* = 28.1 Hz), 161.4 (t, *J* = 30.0 Hz), 161.2, 135.9, 133.2, 132.0 (q, *J* = 33.7 Hz), 131.6 (m), 129.9, 126.9 (q, *J* = 3.3 Hz), 123.4 (q, *J* = 271.2 Hz), 109.8 (t, *J* = 263.7 Hz), 106.3, 101.0, 69.3, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.5 (s, 2 F), –63.1 (s, 3 F). IR (film) 2962, 2843, 1778, 1713, 1612, 1599, 1462, 1433, 1337, 1207, 1159, 1134, 1074, 939, 924, 839, 692, 652 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{15}F_5O_5$ $[M]^+$ 418.0840, found 418.0838.



3.6c

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

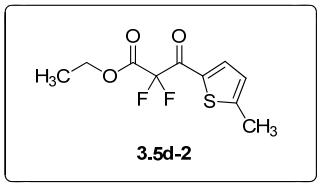
General procedure C was followed using **3.5c** (209 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). The reaction was run at 130 °C for 24 h. Workup and chromatographic purification (1% to 10% CH_2Cl_2 in hexanes) afforded the title compound **3.6c** as a colorless oil (144 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 6.45 (d, *J* = 2.0 Hz, 2 H), 6.40 (t, *J* = 2.2 Hz, 1 H), 3.77 (s, 6 H), 3.47 (t, *J* = 17.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.8 (t, *J* = 31.2 Hz), 160.9, 133.3 (t, *J* = 3.7 Hz), 133.0 (t, *J* = 3.1 Hz), 132.9 (t, *J* = 2.5 Hz), 131.5 (t, *J* = 32.9 Hz), 130.7 (q, *J* = 3.3 Hz), 129.5, 127.1 (h, *J* = 3.7 Hz), 123.6 (q, *J* = 270.9 Hz), 118.4 (t, *J* = 253.1 Hz), 109.1, 99.9, 55.5, 40.4 (t, *J* = 22.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.2 (t, *J* = 16.9 Hz, 2 F), –63.0 (s, 3 F). IR (film) 3003, 2941, 2841, 1713, 1610, 1597, 1464, 1431, 1335, 1259, 1205, 1165, 1132, 1074, 837, 816, 766, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_5O_3$ $[M+H]^+$ 375.1020, found 375.1022.



3.5d-3

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

General procedure D was followed using activated Zn (1.94 g, 29.6 mmol), 1,2-dibromoethane (0.15 mL, 1.8 mmol), 5-methyl-2-thiophenecarboxaldehyde (1.6 mL, 15 mmol), ethyl bromodifluoroacetate (1.9 mL, 15 mmol), and THF (0.030 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.5d-3** as a yellow oil (2.15 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, *J* = 3.2 Hz, 1 H), 6.68 (dd, *J* = 3.4, 1.4 Hz, 1 H), 5.33 (ddd, *J* = 14.8, 8.0, 6.4 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 2.60 (d, *J* = 6.0 Hz, 1 H), 2.49 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.4 (dd, *J* = 32.5, 31.2 Hz), 142.2, 134.2, 128.0, 125.3, 113.4 (dd, *J* = 257.5, 253.8 Hz), 70.6 (dd, *J* = 27.5, 25.0 Hz), 63.5, 15.5, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.2 (dd, *J* = 263.2, 15.0 Hz, 1 F), –114.2 (dd, *J* = 263.2, 7.5 Hz, 1 F). IR (film) 3495, 2986, 2924, 1759, 1375, 1321, 1217, 1186, 1103, 1072, 1045, 854, 793, 669 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_{12}F_2O_3SNa$ $[M+Na]^+$ 273.0373, found 273.0376.

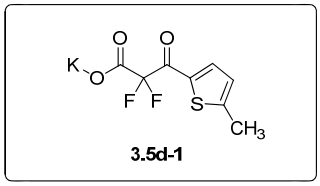


3.5d-2

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

General procedure E was followed using oxalyl chloride (3.9 mL, 46 mmol), DMSO (4.4 mL, 61 mmol), **3.5d-3** (3.8 g, 15 mmol), Et_3N (13 mL, 92 mmol) and CH_2Cl_2 (0.11 L). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.5d-2** as a yellow oil (3.2 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87–7.86 (m, 1 H), 6.90 (dd, *J* = 4.2, 1.4 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.60 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 154.5, 137.4 (t, *J* = 4.4 Hz), 135.3, 128.2, 109.7 (t, *J* = 262.5 Hz), 64.0, 16.4, 14.1.

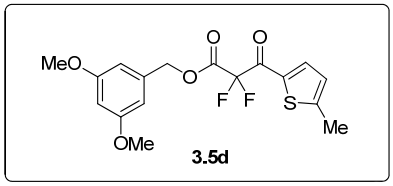
^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.2 (s, 2 F). IR (film) 2988, 2941, 1774, 1666, 1446, 1313, 1267, 1157, 1126, 1053, 868, 816, 787, 675, 580 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_{10}F_2O_3SNa$ $[M+Na]^+$ 271.0216, found 271.0221.



3.5d-1

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

General procedure F was followed using **3.5d-2** (3.0 g, 12 mmol), KOH (0.67 g, 12 mmol), and MeOH (25 mL). Workup afforded the title compound **3.5d-1** as a colorless solid (2.6 g, 84%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.78 (d, J = 3.6 Hz, 1 H), 6.97 (dd, J = 4.0, 1.4 Hz, 1 H), 2.52 (s, 3 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 182.6 (t, *J* = 28.8 Hz), 162.1 (t, *J* = 23.8 Hz), 150.9, 136.8, 136.2 (t, *J* = 2.5 Hz), 127.8, 111.3 (t, *J* = 261.9 Hz), 15.6. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –105.2 (s, 2 F). IR (film) 1693, 1668, 1454, 1389, 1298, 1157, 1130, 1074, 1047, 860, 818, 806, 793, 706, 615, 590, 575, 511 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_8H_5F_2K_2O_3S$ $[M+K]^+$ 296.9202, found 296.9193. mp 141–142 °C decomposed.

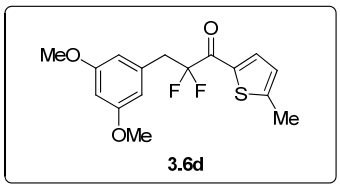


3.5d

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

General procedure G was followed using potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate **3.5d-1** (1.1 g, 4.1 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), 3,5-dimethoxybenzyl alcohol (0.66 g, 3.9 mmol), Et_3N (0.96 mL, 6.9 mmol), DMF (0.13 mL), and CH_2Cl_2 (22 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **3.5d** as a light yellow oil (0.49 g, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (dt, *J* = 4.0, 1.6 Hz, 1 H), 6.86 (dd, *J* = 4.0, 1.2 Hz, 1 H), 6.46 (d, *J* = 2.0 Hz, 2 H), 6.42 (t, *J* = 2.2 Hz, 1 H), 5.28 (s, 2 H), 3.78 (s, 6 H), 2.58 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9 (t, *J* = 28.1 Hz), 161.7 (t, *J* = 30.6 Hz), 161.1, 154.6, 137.4 (t, *J*

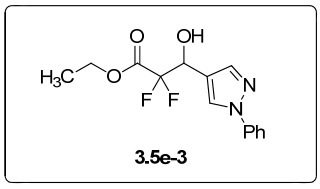
= 4.4 Hz), 136.2, 135.1 (t, *J* = 1.9 Hz), 128.2, 109.7 (t, *J* = 263.7 Hz), 106.0, 101.1, 69.0, 55.6, 16.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.0 (s, 2 F). IR (film) 2960, 2939, 2841, 1774, 1670, 1599, 1448, 1302, 1205, 1155, 1053, 918, 837, 816, 750, 700, 677 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{16}F_2O_5SNa$ $[M+Na]^+$ 393.0584, found 393.0577.



3.6d

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

General procedure C was followed using **3.5d** (185 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.6d** as an off-white solid (137 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.74 (m, 1 H), 6.83 (d, *J* = 4.0 Hz, 1 H), 6.44 (s, 2 H), 6.39 (t, *J* = 2.2 Hz, 1 H), 3.77 (s, 6 H), 3.41 (t, *J* = 17.4 Hz, 2 H), 2.56 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.4 (t, *J* = 30.6 Hz), 160.8, 153.2, 136.9 (t, *J* = 5.6 Hz), 136.5, 133.4 (t, *J* = 3.7 Hz), 127.9, 118.3 (t, *J* = 253.1 Hz), 109.0, 99.9, 55.5, 40.8 (t, *J* = 23.1 Hz), 16.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –99.7 (t, *J* = 18.8 Hz, 2 F). IR (film) 2939, 2839, 1668, 1597, 1446, 1319, 1288, 1205, 1153, 1067, 893, 837, 816, 766, 696, 602 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{16}F_2O_3SNa$ $[M+Na]^+$ 349.0686, found 349.0699. mp 30–31 °C.

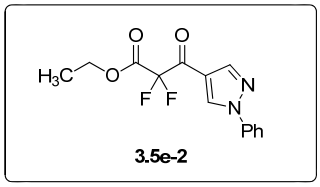


3.5e-3

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

General procedure D was followed using activated Zn (1.54 g, 23.6 mmol), 1,2-dibromoethane (0.16 mL, 1.9 mmol), 1-phenyl-1*H*-pyrazole-4-carbaldehyde[15] (2.70 g, 15.7 mmol), ethyl bromodifluoroacetate (2.0 mL, 15.7 mmol), and THF (80 mL). Workup and chromatographic purification (10% to 30% EtOAc in

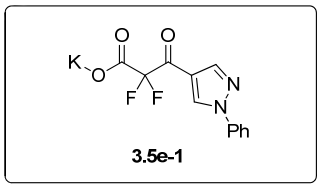
hexanes) afforded the title compound **3.5e-3** as a colorless solid (3.8 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (s, 1 H), 7.74 (s, 1 H), 7.63 (dt, *J* = 7.2, 1.5 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.30 (tt, *J* = 7.6, 1.4 Hz, 1 H), 5.25 (ddd, *J* = 16.0, 7.8, 2.4 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.40 (br, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.6 (t, *J* = 31.2 Hz), 140.3, 139.6, 129.6, 127.1, 127.0, 119.5, 118.2 (d, *J* = 2.5 Hz), 113.9 (dd, *J* = 256.2, 252.5 Hz), 66.9 (dd, *J* = 29.4, 24.4 Hz), 63.3, 13.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.7 (dd, J = 263.2, 15.0 Hz, 1 F), –114.1 (dd, *J* = 263.2, 7.5 Hz, 1 F). IR (film) 3325, 2986, 1759, 1599, 1568, 1504, 1406, 1321, 1213, 1074, 1007, 955, 856, 800, 758, 690 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{14}H_{14}F_2N_2O_3Na$ $[M+Na]^+$ 319.0870, found 319.0865. mp 51–52 °C.



3.5e-2

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

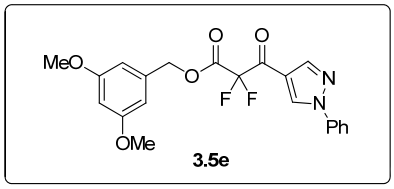
IBX (3.89 g, 13.9 mmol) was added into a solution of compound **3.5e-3** (1.65 g, 5.57 mmol) dissolved in DMSO (0.020 L), and the solution was stirred at rt for 20 h. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (2 x 60 mL) and brine (2 x 60 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (10% to 20% EtOAc in hexanes) provided the title compound **3.5e-2** as a colorless solid (1.45g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1 H), 8.30 (s, 1 H), 7.76–7.73 (m, 2 H), 7.55–7.50 (m, 2 H), 7.43 (tt, *J* = 7.6, 1.5 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.1 (t, *J* = 28.8 Hz), 161.8 (t, *J* = 30.6 Hz), 142.9 (t, *J* = 2.5 Hz), 139.0, 131.6 (t, *J* = 4.4 Hz), 129.9, 128.5, 120.2, 118.8 (t, *J* = 2.5 Hz), 109.5 (t, *J* = 261.9 Hz), 64.1, 14.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –110.8 (s, 2 F). IR (film) 3138, 2986, 1772, 1690, 1541, 1504, 1312, 1244, 1174, 1126, 1036, 951, 889, 824, 760, 688 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{14}H_{12}F_2N_2O_3Na$ $[M+Na]^+$ 317.0714, found 317.0695. mp 28–29 °C.



3.5e-1

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

General procedure F was followed using **3.5e-2** (1.31 g, 4.45 mmol), KOH (0.250 g, 4.45 mmol), and MeOH (0.020 L). Workup afforded the title compound **3.5e-1** as a colorless solid (1.2 g, 89%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.04 (s, 1 H), 8.20 (s, 1 H), 7.90 (dd, J = 7.6, 1.6 Hz, 2 H), 7.55 (t, J = 8.0 Hz, 2 H), 7.41 (t, J = 7.2 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 184.5 (t, J = 28.8 Hz), 162.3 (t, J = 2.5 Hz), 142.3, 138.7, 131.8, 129.7, 127.7, 120.4, 119.4, 111.3 (t, J = 261.2 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3126, 1693, 1682, 1543, 1506, 1385, 1267, 1167, 1126, 1084, 951, 883, 810, 752, 698, 683, 656 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_7F_2K_2N_2O_3$ $[M+K]^+$ 342.9699, found 342.9707. mp 139–140 °C.

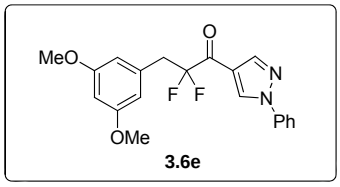


3.5e

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

General procedure G was followed using potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1*H*-pyrazol-4-yl)propanoate **3.5e-1** (1.1 g, 3.7 mmol), oxalyl chloride (0.30 mL, 3.5 mmol), 3,5-dimethoxybenzyl alcohol (0.59 g, 3.5 mmol), Et_3N (0.97 mL, 7.0 mmol), DMF (0.13 mL), and CH_2Cl_2 (20 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **3.5e** as an off-white solid (0.42 g, 29%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (s, 1 H), 8.28 (s, 1 H), 7.71–7.69 (m, 2 H), 7.52 (t, J = 8.0 Hz, 2 H), 7.44–7.40 (m, 1 H), 6.46 (d, J = 2.4 Hz, 2 H), 6.39 (t, J = 2.2 Hz, 1 H), 5.28 (s, 2 H), 3.75 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.8 (t, J = 29.4 Hz), 161.6 (t, J = 31.2 Hz), 161.2, 143.0 (t, J = 2.5 Hz), 138.9, 136.0, 131.6 (t, J = 3.7 Hz), 129.9, 128.6, 120.2, 118.7, 109.5 (t, J = 262.5 Hz), 106.2, 101.0, 69.2, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –110.7 (s, 2 F). IR (film) 3134, 2959, 2941,

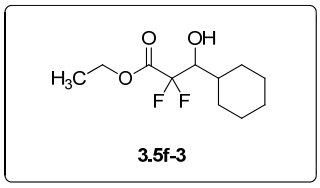
2841, 1774, 1686, 1599, 1541, 1502, 1466, 1431, 1381, 1302, 1242, 1205, 1157, 1068, 1036, 951, 881, 820, 760, 688, 660, 607 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{18}F_2N_2O_5Na$ $[M+Na]^+$ 439.1081, found 439.1061. mp 66–67 °C.



3.6e

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

General procedure C was followed using **3.5e** (208 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (2.5% to 5% EtOAc in hexanes) afforded the title compound **3.6e** as an off-white solid (127 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1 H), 8.21 (s, 1 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.42–7.37 (m, 1 H), 6.46 (d, *J* = 2.0 Hz, 2 H), 6.37 (t, *J* = 2.2 Hz, 1 H), 3.76 (s, 6 H), 3.42 (t, *J* = 17.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.5 (t, *J* = 31.9 Hz), 160.9, 143.1 (t, *J* = 2.5 Hz), 139.1, 133.3 (t, *J* = 3.7 Hz), 131.5 (t, *J* = 5.0 Hz), 129.9, 128.3, 120.1, 119.8 (t, *J* = 2.5 Hz), 118.3 (t, *J* = 251.9 Hz), 109.1, 99.8, 55.5, 40.4 (t, *J* = 23.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –101.8 (t, *J* = 16.9 Hz, 2 F). IR (film) 2939, 2839, 1682, 1597, 1539, 1504, 1464, 1431, 1296, 1205, 1151, 1070, 1038, 951, 874, 845, 760, 688 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, found 373.1352. mp 58–59 °C.

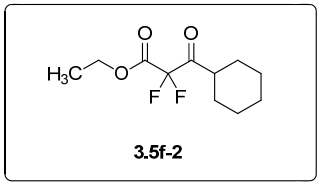


3.5f-3

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

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), cyclohexanecarboxaldehyde (3.0 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded

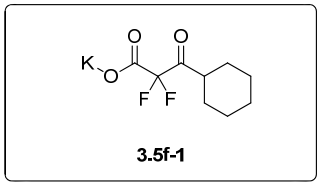
the title compound **3.5f-3** as a colorless oil (3.7 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (q, *J* = 7.2 Hz, 2 H), 3.89–3.79 (m, 1 H), 1.99 (d, *J* = 8.0 Hz, 1 H), 1.94–1.91 (m, 1 H), 1.82–1.65 (m, 5 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.32–1.08 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (dd, *J* = 32.5, 31.2 Hz), 115.6 (dd, *J* = 256.2, 253.8 Hz), 75.4 (dd, *J* = 26.2, 23.8 Hz), 63.2, 38.4, 29.8, 27.5, 26.3, 26.2, 26.0, 14.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –120.1 (dd, *J* = 263.2, 15.0 Hz, 1 F), –111.6 (dd, *J* = 263.2, 7.5 Hz, 1 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_{18}F_2O_3Na$ $[M+Na]^+$ 259.1122, found 259.1128. Spectroscopic data matched that from the previous report.[1]



3.5f-2

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

General procedure E was followed using oxalyl chloride (3.8 mL, 44 mmol), DMSO (4.2 mL, 59 mmol), **3.5f-3** (3.47 g, 14.7 mmol), Et_3N (12 mL, 88 mmol) and CH_2Cl_2 (95 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **3.5f-2** as a colorless oil (3.00 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.37 (q, *J* = 7.2 Hz, 2 H), 2.94–2.88 (m, 1 H), 1.94–1.89 (m, 2 H), 1.85–1.80 (m, 2 H), 1.73–1.69 (m, 1 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.47–1.19 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.4 (t, *J* = 26.2 Hz), 161.8 (t, *J* = 30.6 Hz), 108.8 (t, *J* = 263.1 Hz), 63.8, 45.5, 28.3, 25.7, 25.5, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –113.1 (s, 2 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_{16}F_2O_3Na$ $[M+Na]^+$ 257.0965, found 257.0959. Spectroscopic data matched that from the previous report.[1]

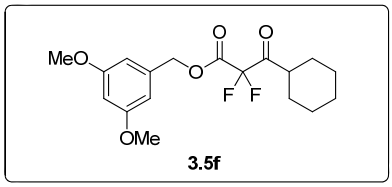


3.5f-1

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

General procedure F was followed using **3.5f-2** (2.8 g, 12 mmol), KOH (0.67 g, 12 mmol), and MeOH (12 mL). Workup afforded the title compound **3.5f-1** as a colorless solid (2.5 g, 85%). ^{1}H NMR (DMSO-

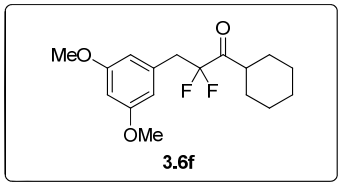
d_6, 400 MHz) δ 2.72–2.66 (m, 1 H), 1.78–1.59 (m, 5 H), 1.27–1.11 (m, 5 H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 204.0 (t, J = 26.2 Hz), 162.2, 111.2 (t, J = 263.8 Hz), 44.8, 28.3, 25.4, 25.0. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –111.1 (s, 2 F). IR (film) 2935, 2864, 1732, 1690, 1674, 1446, 1373, 1329, 1248, 1207, 1174, 1140, 1070, 964, 820, 796, 739, 631, 584 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_9H_{11}F_2K_2O_3$ $[M+K]^+$ 282.9950, found 282.9948. mp 188 °C decomposed.



3.5f

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

General procedure G was followed using potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate **3.5f-1** (0.93 g, 3.8 mmol), oxalyl chloride (0.31 mL, 3.7 mmol), 3,5-dimethoxybenzyl alcohol (0.54 g, 3.2 mmol), Et_3N (0.89 mL, 6.4 mmol), DMF (0.12 mL), and CH_2Cl_2 (20 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **3.5f** as a colorless oil (0.74 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.49 (d, J = 2.0 Hz, 2 H), 6.45 (t, J = 2.4 Hz, 1 H), 5.26 (s, 2 H), 3.80 (s, 6 H), 2.90–2.84 (m, 1 H), 1.86 (dd, J = 13.6, 2.8 Hz, 2 H), 1.81–1.76 (m, 2 H), 1.71–1.66 (m, 1 H), 1.44–1.19 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.2 (t, J = 26.9 Hz), 161.7 (t, J = 30.6 Hz), 161.2, 136.2, 108.8 (t, J = 263.1 Hz), 106.2, 101.1, 68.9, 55.6, 45.5, 28.2, 25.6, 25.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –112.9 (s, 2 F). IR (film) 2937, 2856, 1780, 1736, 1599, 1458, 1431, 1379, 1302, 1207, 1155, 1068, 970, 955, 837, 702, 588 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{22}F_2O_5Na$ $[M+Na]^+$ 379.1333, found 379.1324.

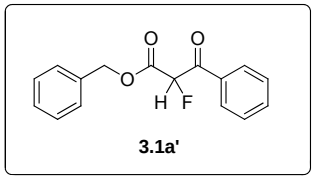


3.6f

2-(methylthio)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.6f)

General procedure C was followed using **3.5f** (178 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). The reaction was run at 130 °C for 24 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **3.6f** as a colorless oil (92 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.39–6.37 (m, 3 H), 3.78 (s, 6 H), 3.25 (t, *J* = 16.8 Hz, 2 H), 2.73–2.67 (m, 1 H), 1.76–1.64 (m, 5 H), 1.29–1.19 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6 (t, *J* = 29.4 Hz), 160.9, 133.3 (t, *J* = 4.4 Hz), 117.8 (t, *J* = 253.7 Hz), 108.9, 99.9, 55.5, 45.3, 39.9 (t, *J* = 23.1 Hz), 28.1, 25.8, 25.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.5 (t, *J* = 16.9 Hz, 2 F). IR (film) 2935, 2856, 1732, 1608, 1599, 1462, 1431, 1310, 1296, 1205, 1153, 1070, 980, 930, 891, 837, 760 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3SNa$ $[M+Na]^+$ 359.0529, found 359.0511.

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

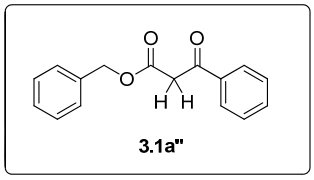


3.1a'

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

Compound **3.1′** was prepared according to a previous report.[16] Compound **3.1a″** (1.87 g, 7.35 mmol) and $CpTiCl_3$ (81.0 mg, 0.370 mmol) were dissolved in CH_3CN (0.040 L) at rt, and selectfluor (2.86 g, 8.08 mmol) was added. The mixture was stirred at rt for 6 h, and filtered to remove solids. The filtrate was concentrated, and the crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **3.1a′** as a colorless oil (1.71 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.64 (tt, *J* = 7.6, 1.5 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.34–7.30 (m, 3 H), 7.28–7.25 (m, 2 H), 5.93 (d, *J* = 48.8 Hz, 1 H), 5.31–5.23 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.5 (d, *J* = 20.0 Hz), 165.0 (d, *J* = 25.0 Hz), 134.8, 134.5, 133.5 (d, *J* = 1.2 Hz), 129.7 (d, *J* = 2.5 Hz), 129.0, 128.9, 128.8, 128.5, 90.2 (d, *J* = 196.2 Hz), 68.3. ^{19}F NMR ($CDCl_3$, 376

MHz) δ –190.4 (d, J = 45.1 Hz, 1 F). IR (film) 3065, 3034, 2957, 1765, 1693, 1597, 1580, 1499, 1450, 1381, 1283, 1240, 1213, 1184, 1101, 957, 744, 694, 606 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{13}FO_3Na$ $[M+Na]^+$ 295.0746, found 295.0757.



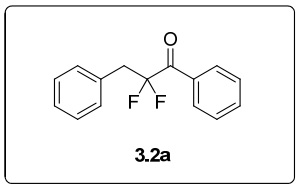
3.1a"

benzyl 3-oxo-3-phenylpropanoate (3.1a″)

Compound **3.1a″** was prepared according to a previous report.[17] A mixture of benzyl alcohol (1.0 mL, 10.0 mmol), ethyl benzoylacetate (1.73 g, 10.0 mmol), DMAP (1.22 g, 10.0 mmol) was stirred with oven-dried 4 Å molecular sieves (50 g) in dry toluene (0.080 L) at 100–105 °C for 36 h. The reaction mixture was cooled to rt, and filtered to remove the molecular sieves. The solvents were removed under reduced pressure, and EtOAc (60 mL) and water (60 mL) were added to the residue. The layers were separated, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **3.1a″** as a as a yellow solid (2.1 g, 83%, ketone : enol = 4.4:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 12.51 (s, 1 H, enol), 7.95–7.93 (m, 2 H, keto), 7.80–7.78 (m, 2 H, enol), 7.63–7.58 (m, 1 H, keto), 7.50–7.30 (m, 15 H, keto + enol), 5.75 (s, 1 H, enol), 5.27 (s, 2 H, enol), 5.21 (s, 2 H, keto), 4.06 (s, 2 H, keto). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.5 (keto), 173.1 (enol), 172.0 (enol), 167.6 (keto), 136.1, 136.0, 135.5, 134.0, 133.5, 131.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 126.3, 87.4 (enol), 67.4 (keto), 66.3 (enol), 46.2 (keto). IR (film) 3063, 3032, 2957, 1742, 1688, 1637, 1497, 1450, 1410, 1325, 1267, 1211, 1186, 1144, 1078, 980, 775, 754, 688, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}O_3Na$ $[M+Na]^+$ 277.0841, found 277.0833. mp 39–40 °C.

Experimental Procedures and Characterization of Compounds for Table 3.3

General Procedure H: An oven-dried 20 mL scintillation vial was charged with substrate (**3.1a**, **3.1a′** or **3.1a″**, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry *o*-xylene (0.010 L) was added *via* a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 120 °C, and stirred for 15 h. The vial was cooled to rt, and the mixture was diluted with EtOAc. An internal standard was added, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing in prior to ^{19}F or ^{1}H NMR analysis.



3.2a

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

General procedure H was followed using **3.1a** (145 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and *o*-xylene (0.010 L). Workup and chromatographic purification (0% to 2% EtOAc in hexanes) afforded the title compound **3.2a** as a colorless oil, which becomes a colorless solid in the fridge (100 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.32 (br, 5 H), 3.53 (t, J = 17.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.7 (t, J = 30.6 Hz), 134.4, 132.3 (t, J = 2.5 Hz), 131.5 (t, J = 3.1 Hz), 131.1, 130.3 (t, J = 3.7 Hz), 128.8, 128.6, 127.8, 118.6 (t, J = 253.1 Hz), 40.3 (t, J = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.6 (t, J = 16.9 Hz, 2 F). IR (film) 3063, 3032, 2937, 1701, 1597, 1497, 1450, 1279, 1173, 1115, 1084, 1049, 1032, 943, 901, 727, 715, 698, 669, 600 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{12}F_2ONa$ $[M+Na]^+$ 269.0754, found 269.0742. mp 45 °C. Spectroscopic data matched that from the previous report.[4]

References for Chapter 3 Experimental Section

[1] Linderman, R. J.; Graves, D. M. "Oxidation of Fluoroalkyl-Substituted Carbinols by the Dess-Martin Reagent" *J. Org. Chem*. **1989**, *54*, 661–668.

[2] Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. "Selective and Effective Fluorination of Organic Compounds in Water Using Selectfluor F-TEDA-BF_4" *Org. Lett*. **2004**, *6*, 4973–4976.

[3] We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed decarboxylative difluorobenzylation reactions, including Table S1 to Table S6.

[4] Pravst, I.; Zupan, M.; Stavber, S. "Efficient Synthesis of α,α-difluoro Ketones Using Selectfluor F-TEDA-BF_4" *Synthesis* **2005**, 3140–3146.

[5] Koren-Selfridge, L.; Londino, H. N.; Vellucci, J. K.; Simmons, B. J.; Casey, C. P.; Clark, T. B. "A Boron-Substituted Analogue of the Shvo Hydrogenation Catalyst: Catalytic Hydroboration of Aldehydes, Imines, and Ketones" *Organometallics* **2009**, *28*, 2085–2090.

[6] Naimi-Jamal, M. R.; Hamzeali, H.; Mokhtari, J.; Boy, J.; Kaupp, G. "Sustainable Synthesis of Aldehydes, Ketones or Acids from Neat Alcohols Using Nitrogen Dioxide Gas, and Related Reactions" *ChemSusChem* **2009**, *2*, 83–88.

[7] Liu, L.; Yu, M.; Wayland, B. B.; Fu, X. "Aerobic Oxidation of Alcohols Catalyzed by Rhodium(III) Porphyrin Complexes in Water: Reactivity and Mechanistic Studies" *Chem. Commun*. **2010**, *46*, 6353–6355.

[8] Boije af Gennas, G.; Talman, V.; Aitio, O.; Ekokoski, E.; Finel, M.; Tuominen, R. K.; Yli-Kauhaluoma, J. "Design, Synthesis, and Biological Activity of Isophthalic Acid Derivatives Targeted to the C1 Domain of Protein Kinase C" *J. Med. Chem*. **2009**, *52*, 3969–3981.

[9] Zhang, C.-P.; Cai, J.; Zhou, C.-B.; Wang, X.-P.; Zheng, X.; Gu, Y.-C.; Xiao, J.-C. "Copper-Mediated Trifluoromethylation of Arylboronic Acids by Trifluoromethyl Sulfonium Salts" *Chem. Commun*. **2011**, *47*, 9516–9518.

[10] (a) Castro, L. C. M.; Bézier, D.; Sortais, J.-B.; Darcel, C. "Iron Dihydride Complex as the Pre-Catalyst for Efficient Hydrosilylation of Aldehydes and Ketones under Visible Light Activation" *Adv. Synth. Catal*. **2011**, *353*, 1279–1284. (b) Ashley, J. N.; Barber, H. J.; Ewins, A. J.; Newbery, G.; Self, A. D. H. "Chemotherapeutic Comparison of the Trypanocidal Action of Some Aromatic Diamidines" *J. Chem. Soc.* **1942**, 103–116.

[11] Zhang, L.; Wang, S.; Zhou, S.; Yang, G.; Sheng, E. "Cannizzaro-Type Disproportionation of Aromatic Aldehydes to Amides and Alcohols by Using Either a Stoichiometric Amount or a Catalytic Amount of Lanthanide Compounds" *J. Org. Chem*. **2006**, *71*, 3149–3153.

[12] Zhou, H.; Xu, Q.; Chen, P. "Kinetic Resolution of 2,2-Difluoro-3-hydroxy-3-aryl-propionates Catalyzed by Organocatalyst (*R*)-Benzotetramisole" *Tetrahedron* **2008**, *64*, 6494–6499.

[13] Mei, Z.-W.; Omote, T.; Mansour, M.; Kawafuchi, H.; Takaguchi, Y.; Jutand, A.; Tsuboi, S.; Inokuchi, T. "A High Performance Oxidation Method for Secondary Alcohols by Inductive Activation of TEMPO in Combination with Pyridine-Bromine Complexes" *Tetrahedron* **2008**, *64*, 10761–10766.

[14] Fuqua, S. A.; Parkhurst, R. M.; Silverstein, R. M. "Synthesis and Chemistry of Several Fluorinated *p*-Xylenes Designed as Precursors for α,α,α′,α′-Tetrafluoro-*p*-xylylene" *Tetrahedron* **1964**, *20*, 1625–1632.

[15] de Oliveira, C. H. A.; Mairink, L. M.; Pazini, F.; Liao, L. M.; de Oliveira, A. L.; Viegas, C.; de Oliveira, V.; Cunha, L. C.; Oliveria, F. G. F.; Paz, J. L.; Eberlin, M. N.; Menegatti, R. "Chemoselective and Regiospecific Formylation of 1-Phenyl-1*H*-pyrazoles through the Duff Reaction" *Synth. Commun.* **2013**, *43*, 1633–1639.

[16] Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. "Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of β-Ketoesters" *Org. Lett*. **2003**, *5*, 1709–1712.

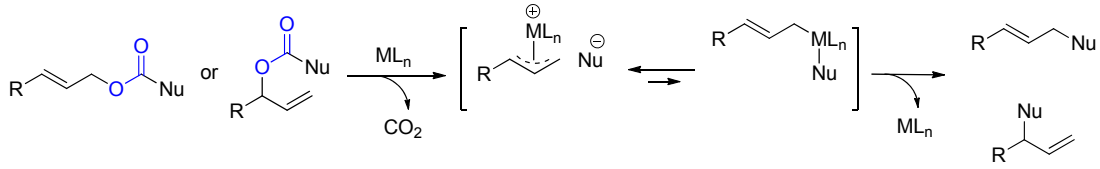
[17] Gilbert, J. C.; Kelly, T. A. "Transesterification of 3-Oxo Esters with Allylic Alcohols" *J. Org. Chem*. **1988**, *53*, 449–450.

Chapter 4. Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation of α,α-Difluoroketone Enolates

4.1 Introduction to Transition Metal-Catalyzed Decarboxylative Allylation

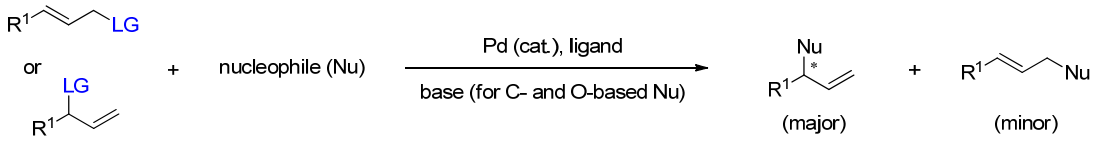
Decarboxylative coupling is a powerful method for the construction of C–C bonds that generates reactive organometallic intermediates under mild conditions and releases CO_2 as the only byproduct.[1] Moreover, this strategy enables the formation of reactive nucleophiles bearing an acidic proton capable of undergoing deprotonation and regioselective coupling to provide products that might be difficult to access otherwise.[2] Among decarboxylative C–C coupling reactions, decarboxylative allylation reactions,[1b] in which the allylic electrophile and the nucleophile are generated *in situ* from unimolecular decarboxylation of β-ketoesters, are broadly investigated because of their potential applications. These types of reaction play an important role in accessing chiral allylic products[3] and are widely applied for the synthesis of natural products (Scheme 4.1).[4]

Scheme 4.1. General Mechanism of Transition Metal-Catalyzed Decarboxylative Allylation Reactions



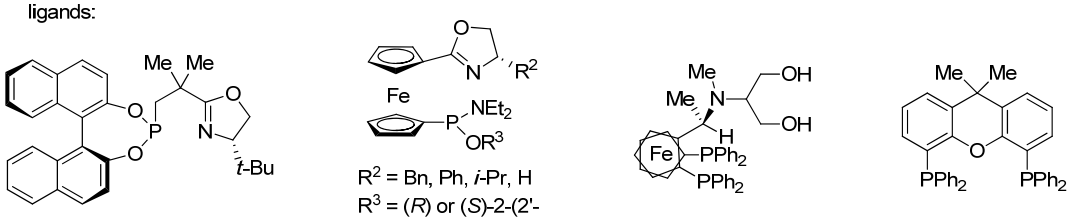
Many transition metals participate in the allylation reactions with complementary regioselectivities. Metals such as Ru, Rh, Ir, Mo, and W afford the branched products,[1b,5] while Pd metal complexes predominately form the linear products.[1b,6] With the development of new ligands, Pd-catalyzed allylation reactions of monosubstituted allylic electrophiles with soft C-based (e.g. malonates, β-diketones, β-ketoestsers) and heteroatom-based nucleophiles can enable to access branched products (Scheme 4.2).[7]

Scheme 4.2. New Ligands Enable to Access Branched Products for Pd-Catalyzed Allylation Reactions



R^1 = aryl, alkenyl, alkyl
LG = OAc, OCO_2Me, OCO_2Et, OBoc
Nu = $CH_2(CO_2Me)$, RCH_2NO_2 (R = alkyl, Ph), $ArCH_2OH$, $PhCH_2NH_2$, $(Boc)_2NH$, Ph_2CNNH_2, Ph_3CONH_2, $BnONH_2$, BnONHBoc, MeONHBoc, 1,2,3,4-tetrahydroisoquinoline

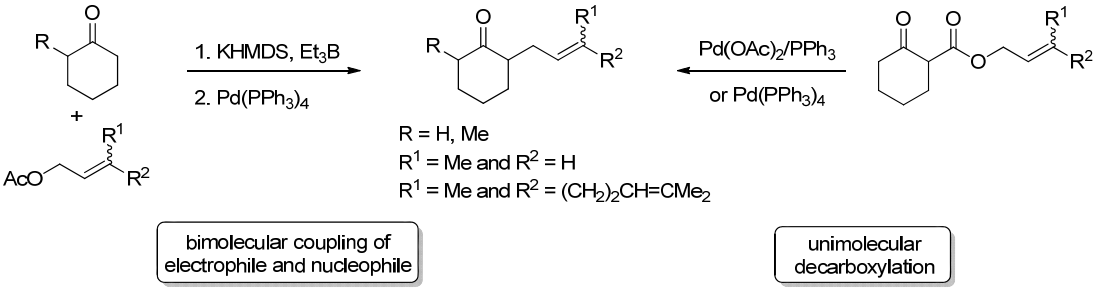
ligands:



R^2 = Bn, Ph, *i*-Pr, H
R^3 = (*R*) or (*S*)-2-(2'-hydroxy-1,1'-bi-naphthyl)

Pd-catalyzed allylation reactions of hard ketone enolate nucleophiles with monosubstituted allylic electrophiles almost exclusively provide linear products (Scheme 4.3),[1b,3c,8] which arise from an outer-sphere attack of enolates on the less-hindered terminus of a Pd-π-allyl intermediate.

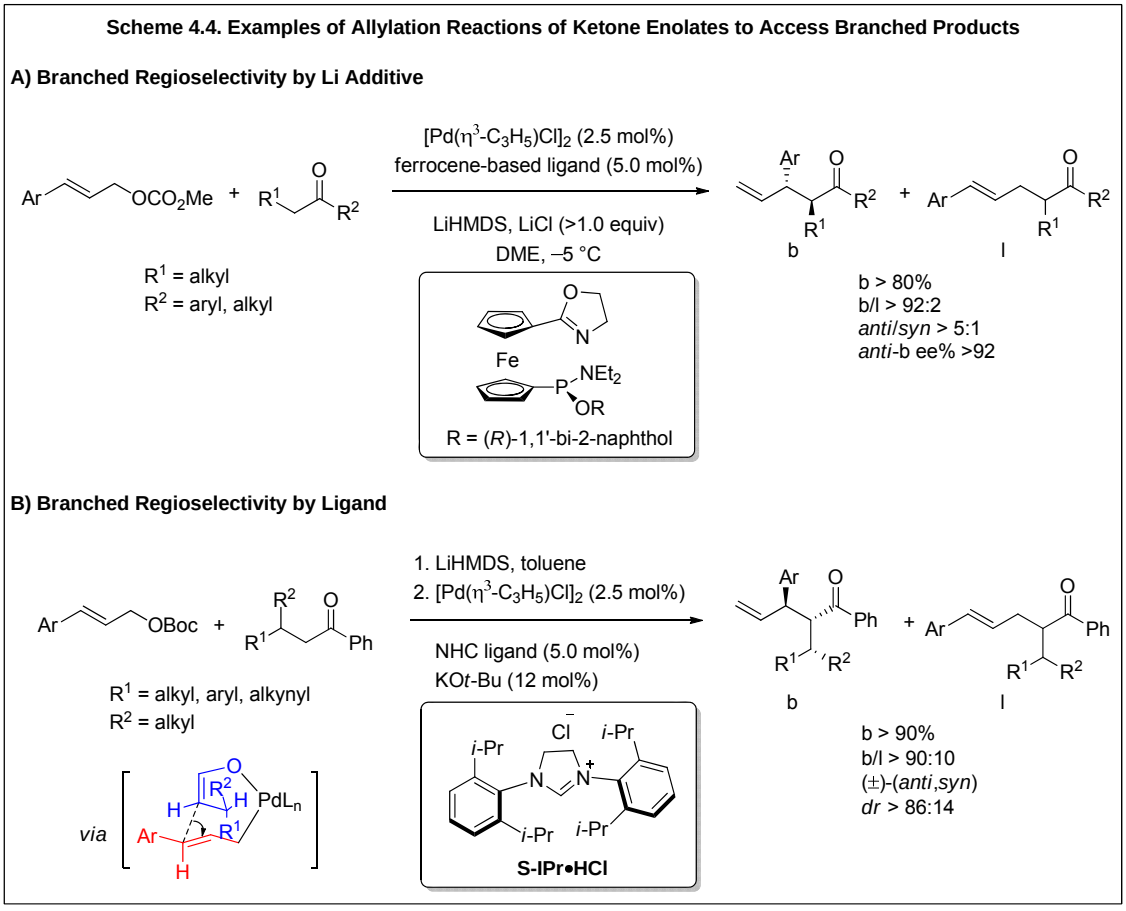
Scheme 4.3. Representative Examples of Allylation Reactions of Ketone Enolates to Access Linear Products



In a rare example, a Pd-catalyzed allylation reaction of a ketone enolate employed stoichiometric Li additives to generate the uncommon branched product (Scheme 4.4A), while the use of Cu(I) salts still favored the formation of linear products.[9] In this reaction, the selectivity was believed to originate from the state of carbanion aggregation, which was affected by the addition of Li or Cu(I) additives. However

until recently, the ability of a ligand to control the regioselectivity for Pd-catalyzed allylation reactions of ketone enolates had not been reported. In 2016, the Hou lab demonstrated a ligand controlled Pd-catalyzed allylation reaction of the ketone enolates to generate the branched products, in which the use of achiral NHC ligands enables the formation of racemic *anti*/*syn* products along with other diastereo-isomers (Scheme 4.4B).[10] In their mechanistic studies, the branched products come from an inner-sphere [3,3′]-reductive elimination based on the experimental results and density functional theory (DFT) calculations.

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

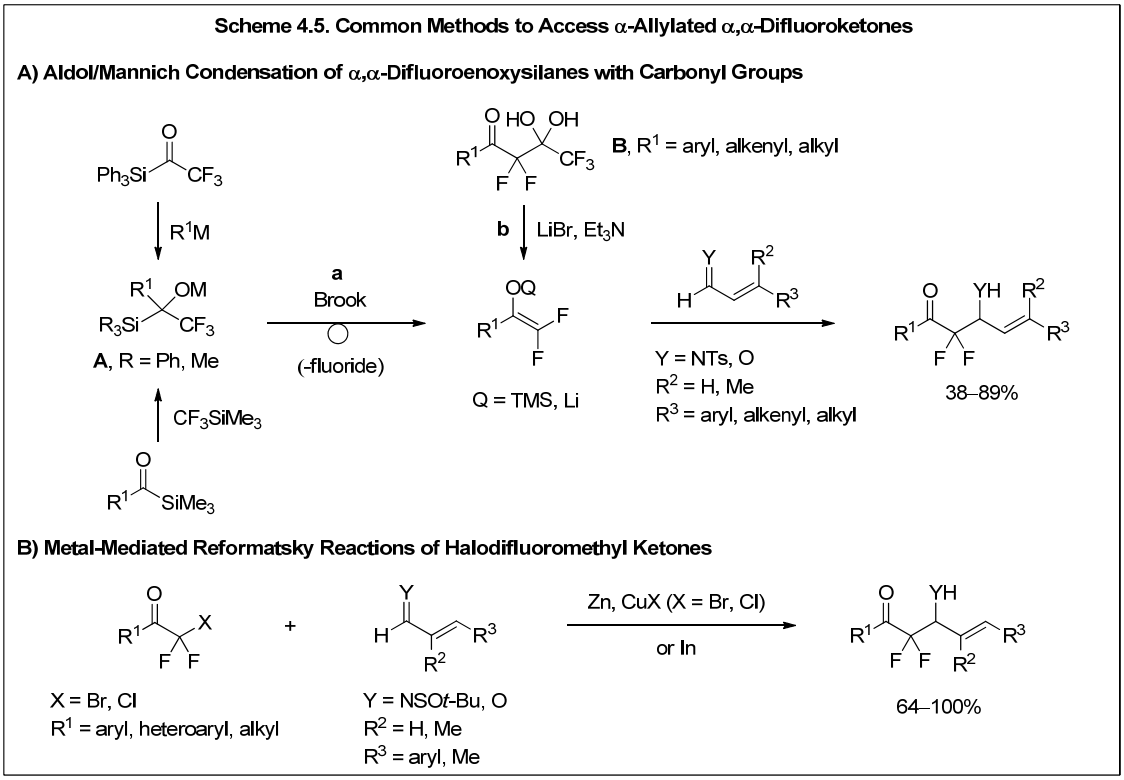


4.2 Development to Access α-Allyl-α,α-Difluoroketones

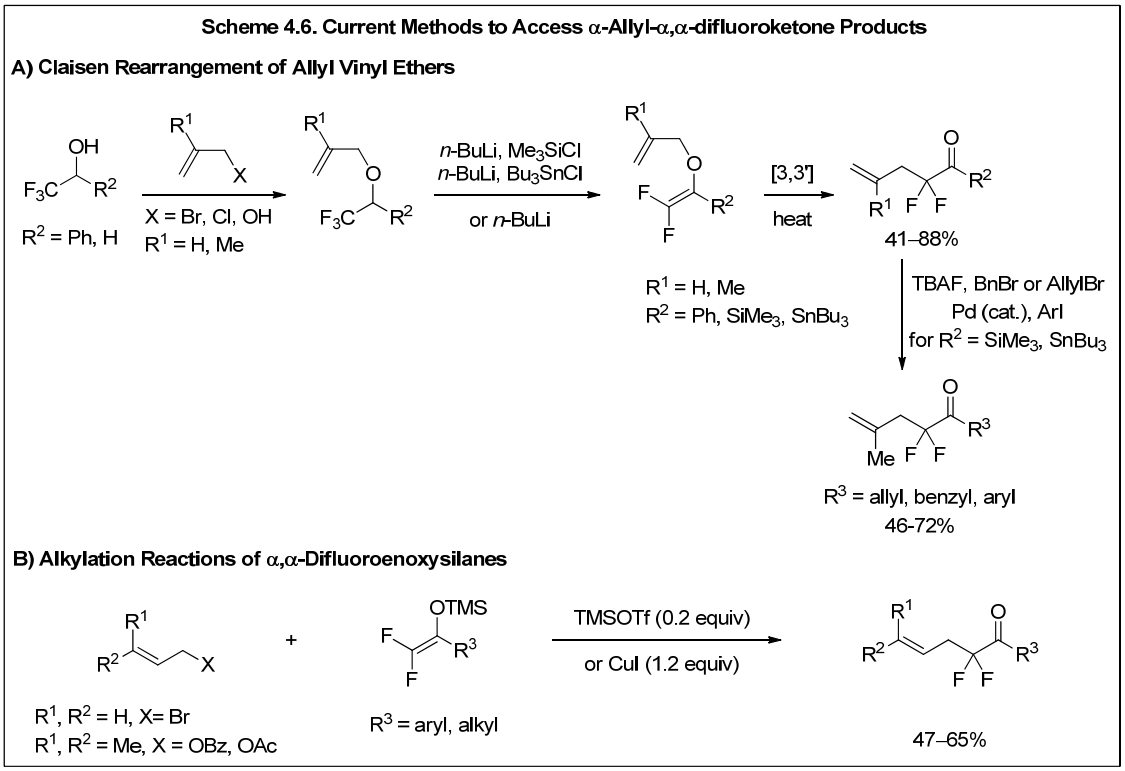
Current methods to access α-allylated α,α-difluoroketones focus on Aldol/Mannich condensation reactions of α,α-difluoroenoxysilanes (Scheme 4.5A),[11] which come from either Brook rearrangement of the intermediate **A** (path a) or trifluoroacetate-release-drived cleavage of a C–C bond of

pentafluoroacetone hydrate **B** (path b). Other similar strategies involve Reformatsky-type reactions of halodifluoromethyl ketones with allylic aldehydes and imines using an excess of metal as a mediator (Scheme 4.5B).[12] However, these reactions simultaneously introduce a heteroatom at the α-position, while also incorporating the allyl group.

Scheme 4.5. Common Methods to Access α-Allylated α,α-Difluoroketones



The Claisen rearrangement has also been utilized for generating α-allyl-α,α-difluoroketones, and the products including difluoroacylsilanes and difluoroacylstannanes can couple with alkyl or aryl electrophiles to form complex α-allyl-α,α-difluoroketone derivatives (Scheme 4.6A).[13] However, the preparation of the allyl vinyl ether starting materials requires the use of strong bases, which restrict the substrate scope of the entire reaction. Additionally, the Portella and Kobayashi labs demonstrated alkylation reactions of α,α-difluoroenoxysilanes with allyl electrophiles; however, Lewis acids or stoichiometric amount of metal additives are required to promote the reactions, and the substrate scope of these reactions is similarly limited to simple alkyl substituents (Scheme 4.6B).[14]



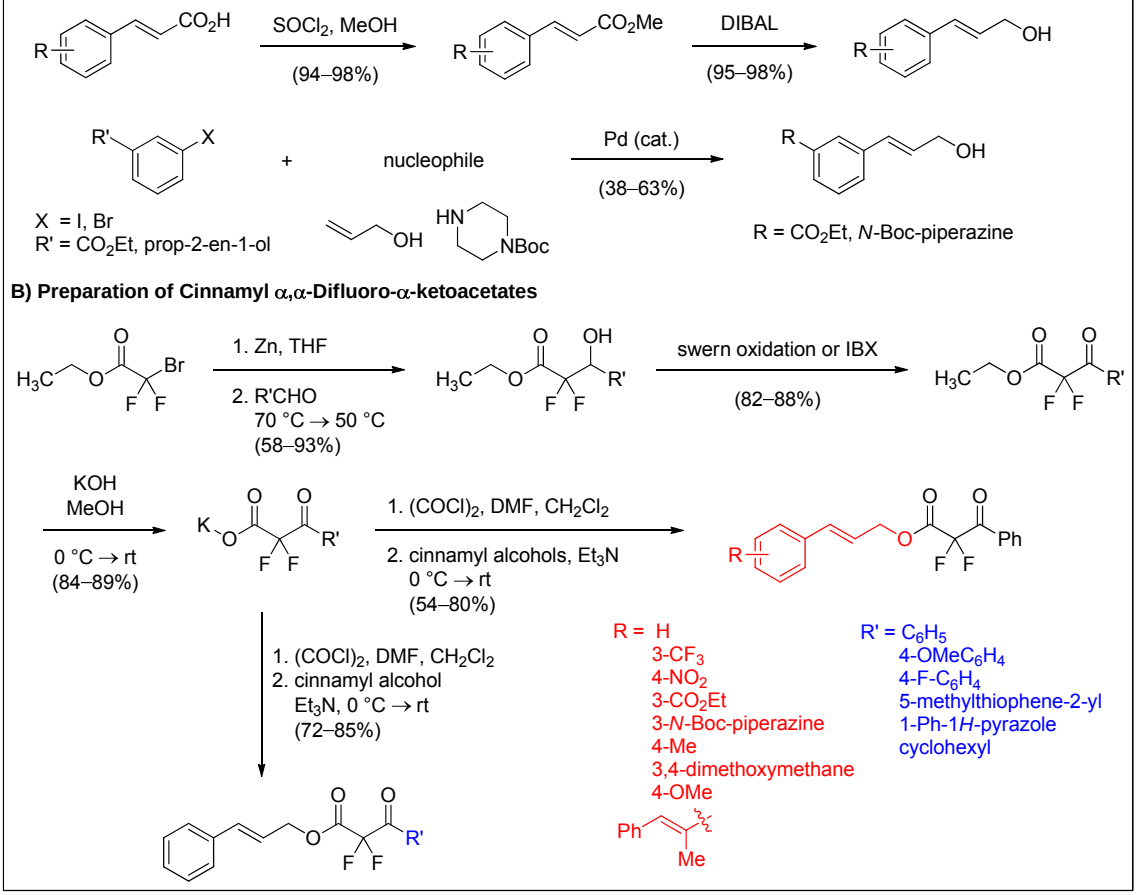
4.3 Palladium-Catalyzed Decarboxylative Difluoroalkylation to Access α-Allyl-α,α-difluoroketones

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

To begin the study, cinnamyl alcohol-derived esters were used as the sp^3-based electrophiles because they possess higher reactivity compared to other allylic electrophiles. The cinnamyl alcohols required were prepared by either reduction of corresponding esters or Pd-catalyzed coupling reactions (Scheme 4.7A). The α,α-difluoroketone enolates would be generated *in situ via* decarboxylation of α,α-difluoro-β-

keto-esters. Thus, cinnamyl α,α-difluoro-β-keto esters were identified as test substrates, and they were prepared through four steps, comprising 1) Reformatsky addition of ethyl bromodifluoroacetate to aldehydes; 2) oxidation of alcohols to ketones; 3) basic hydrolysis of ethyl esters; and 4) the esterification of β-keto-α,α-difluoroacetate with cinnamyl alcohols (Scheme 4.7B).

Scheme 4.7. General Synthetic Sequence for Cinnamyl α,α-Difluoro-β-keto-ester Substrates

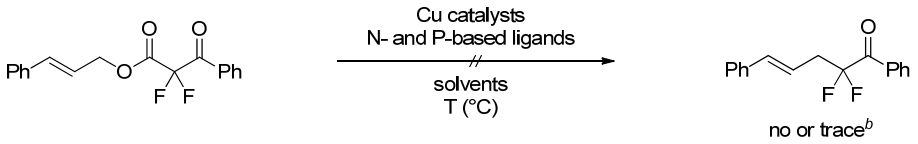


Based on our previous successes with Cu-catalyzed decarboxylative coupling reactions of cinnamyl α-bromo-α,α-difluoro esters, we initially explored the use of Cu-based catalytic systems in decarboxylative allylation reactions of α,α-difluoroketone enolates (Scheme 4.8A). In some of the Cu-catalyzed reactions, full conversion was achieved; however, no or trace amounts of the desired coupling product **4.2a** were detected by GC. Instead, the Cu-based catalysts typically provided difluoroacetophenone and various isomers of bicinnamyl. In contrast, the preliminary result that 5% of

$Pd(OAc)_2/PPh_3$ system provided 5% of the desired coupling product **4.2a** revealed that a Pd-based catalyst could promote the desired transformation (Scheme 4.8B). Thus, Pd-based system was selected for further investigation.

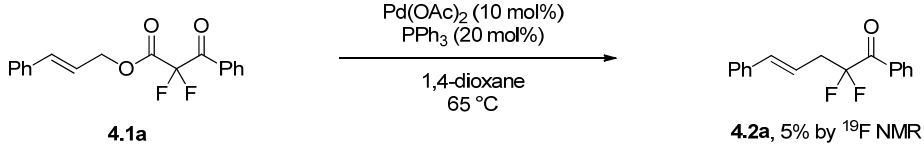
Scheme 4.8. Pd-Based Catalyst Promoted Decarboxylative Allylation of α,α-Difluoroketone Enolates[a]

A) Cu-Based Catalysts Failed to Produce the Desired Products



screening conditions:
Cu catalysts: CuI, CuBr, CuCl, $CuBr_2$, $CuCl_2$, Cu_2O, Cu(Tc), $Cu(OTf)_2$, $Cu(OAc)_2$, $[(CH_3CN)_4Cu]PF_6$, copper (II) 2-ethylhexanoate, chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] copper (I)
N-based ligands: 1,10-phen, 4,7-dimethoxy-1,10-phen, 3,4,7,8-tetramethyl-1,10-phen, bathophenanthroline, 4,5-diazafluoren-9-one, neocuproine, 2,2'-bipyridyl, 4,4'-dimethoxy-2,2'-bipyridyl, 4,4'-di-*tert*-butyl-2,2'-bipyridyl, *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine, *N*,*N*'-dibenzylethylenediamine, TMEDA, DMEDA, *trans*-*N*-(2-pyridylmethylene)aniline, 2-acetylpyridine, chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] copper (I)
P-based ligands: $P(4\text{-}OMeC_6H_4)_3$, P(*o*-Tol)$_3$, Tri(2-furyl)phosphine, DavePhos, XPhos, SPhos, JohnPhos, Xantphos, dppBz, dppe, *rac*-BINAP, dppf
solvents: DMF, CH_3CN, 1,4-dioxane, toluene, 1,2-dichloroethane
T: 40 to 110 °C

B) A Pd-Based Catalyst Enabled the Transformation



4.1a **4.2a**, 5% by ^{19}F NMR

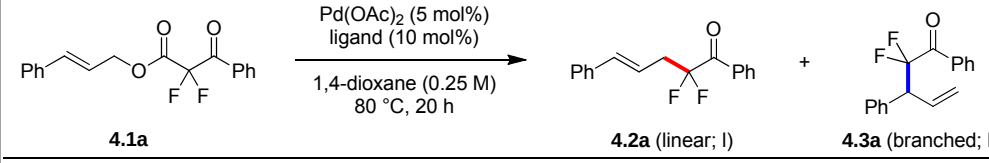
[a] Initial screening was evaluated by GC with dodecane as an internal standard. Once new peaks were observed, then they were checked by GC-Mass. [b] Cu-based catalysts either did not provide the desired coupling product **4.2a** or only generated trace amount of **4.2a** (<5%) based on the comparison of peak integration on GC spectra.

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

A broad screen of P-based ligands identified biarylmonophosphines[17] as privileged ligands for the present reaction. The biarylmonophosphine class of ligands demonstrated several notable relationships between ligand structure and catalytic activity (Scheme 4.9). First, substitution of the *ortho*-position of the right aromatic ring improved the yield and selectivity for the branched product (Scheme 4.9A). For example, only 2% of the branched product was generated with CyJohnPhos; however, the use of SPhos and XPhos improved the yield and selectivity of the transformation. This phenomenon might arise from increased steric hindrance of the ligands, or from inhibition of cyclometalation processes that deactivate the catalyst.[17] Second, substituents on the phosphine atom control the selectivity for formation of branched and linear products (Scheme 4.9B). As a control, XPhos provided a 25:1 selectivity for

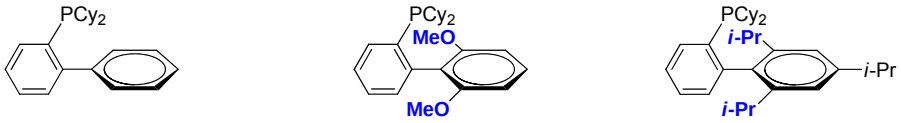
formation of the branched product, and substitution of the cyclohexyl groups with phenyl groups, (PhXPhos)[18] improved the yield and selectivity of the branched product. In contrast, substitution of the cyclohexyl groups with bulkier *t*-butyl groups (*t*-BuXPhos) unexpectedly inverted the regioselectivity and provided an orthogonal protocol for accessing the linear product. Third, relative to *t*-BuXPhos, ligands bearing substituents on the left ring (Me$_4$*t*-BuXPhos and *t*-BuBrettPhos[19]) modulated the yield and selectivity for formation of the linear product (Scheme 4.9C). Additional optimization revealed that both linear and branched products formed in 1,4-dioxane and toluene, although distinct temperatures and concentrations proved optimal for formation of each product.

Scheme 4.9. Structure of Biaryl Monophosphine Ligands Controlled the Regioselectivity of Products



4.1a **4.2a** (linear; l) **4.3a** (branched; b)

A) *Ortho*-Substituents Improved Yield of Branched Product

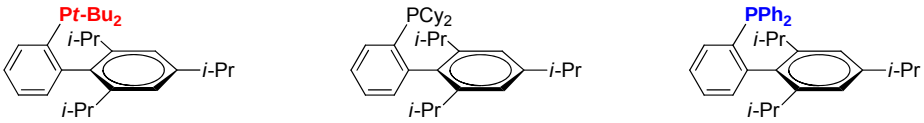


CyJohnPhos — branched: 2%, b/l = 2 : 1

SPhos — branched: 29%, b/l = 15 : 1

XPhos — branched: 25%, b/l = 25 : 1

B) Substituents on P Altered Selectivity of Branched and Linear Products

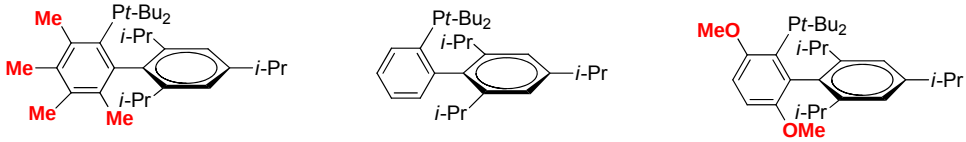


***t*-BuXPhos** — linear: 81%, b/l = 1 : 9

XPhos — branched: 25%, b/l = 25 : 1

PhXPhos — branched: 89%, b/l = 89 : 1

C) Substitutents on Left Ring Altered Yield and Selectivity of Linear Product



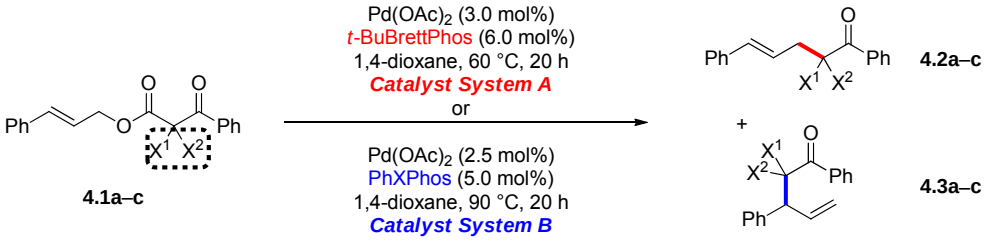
Me$_4$*t*-BuXPhos — linear: 68%, b/l = 1 : 3

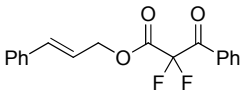
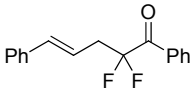
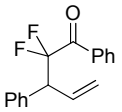
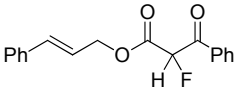
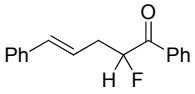
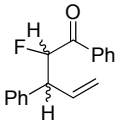
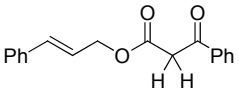
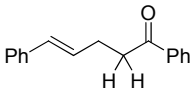
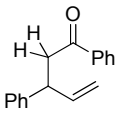
***t*-BuXPhos** — linear: 81%, b/l = 1 : 9

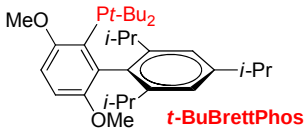
***t*-BuBrettPhos** — linear: 86%, b/l = 1 : 9

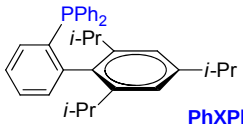
In the present reaction, the ligand-controlled regioselectivity was only observed for the α,α-difluorinated substrate **4.1a** (entry 1, Table 4.1), and the analogous mono- and non-fluorinated substrates (**4.1b** and **4.1c**) did not provide branched products in good yield and regioselectivity (entries 2–3, Table 4.1). Therefore, the physicochemical perturbation resulting from fluorination of the substrate **4.1a** facilitated formation of the branched product. Moreover, the difluorinated substrate **4.1a** operates *via* a decarboxylation followed by allylation mechanism, while the mono- and non-fluorinated substrates (**4.1b** and **4.1c**) might undergo a different mechanism, such as allylation followed by decarboxylation. Thus, the present catalyst systems that operate *via* decarboxylation followed by allylation mechanism may not be appropriate for the transformation of the mono- and non-fluorinated substrates. However, allylation reactions of monofluorinated cyclic-[16] and non-fluorinated cyclic- and acyclic ketone enolates[1b,8–10] have been realized using different catalysts developed by other research groups.

Table 4.1. Ligand-Controlled Regioselective Allylation Reactions of Fluorinated Substrates[a]



entry	substrate	catalyst system A	catalyst system B
1	 **4.1a**	 **4.2a**, 89% (b/l = 1 : 18)	 **4.3a**, 94% (b/l = 99 : 1)
2	 **4.1b**	 **4.2b**, 24% (b/l < 1 : 24)	 **4.3b**, 36% (b/l = 2.1 : 1) (dr, b = 2 : 1)
3	 **4.1c**	 **4.2c**, 85% (b/l < 1 : 50)	 **4.3c**, 5% (b/l = 1 : 2)



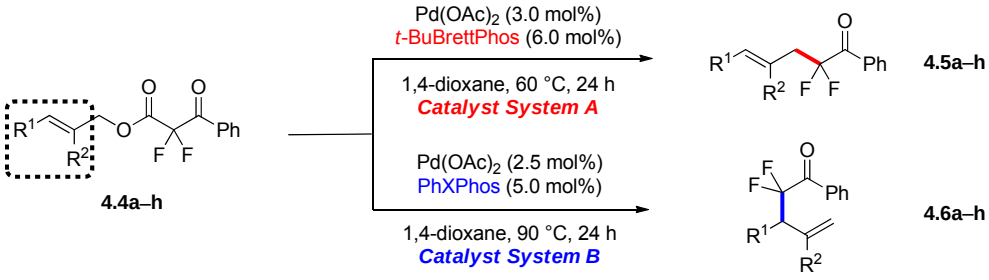


[a] Catalyst System A: substrate (1.0 equiv), $Pd(OAc)_2$ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 20 h; Catalyst System B: substrate (1.0 equiv), $Pd(OAc)_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 20 h. For fluorinated products, yields and selectivities were determined by ^{19}F NMR using $PhCF_3$ or PhF as an internal standard, respectively. For non-fluorinated products, yields and selectivities were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

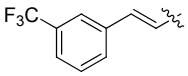
Based on classical reactivity patterns, the ability of α,α-difluoracetophenone to provide both branched and linear products is unexpected. Traditionally for Pd-catalyzed allylation reactions, "hard" and "soft" nucleophiles have been identified by their pK_a values, with hard nucleophiles (pK_a > 25) being less acidic than soft nucleophiles (pK_a < 25).[20] However for most pronucleophiles, the presence of a resonance-stabilizing group lowers the pK_a value and increases the polarizability of the molecular orbitals (e.g. ketone vs. β-ketoester or β-diketone).[1b,21] In contrast for α,α-difluoroketones (pK_a = 20.2),[22] the lower pK_a results from an inductive effect that makes the anions harder (negative fluorine effect).[23] Thus for the present allylation reaction, the α,α-difluoroketone enolates should be harder than acetophenone (pK_a = 24.7),[22] which typically provides linear products.[1b,3c,8] Thus, based on classic hard/soft reactivity trends, the α,α-difluoroketones would not provide the uniquely observed branched product.

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

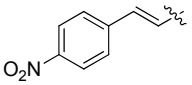
Scheme 4.10. Decarboxylative Difluoroallylation of Substrates Bearing Distinct Allyl Moieties[a]



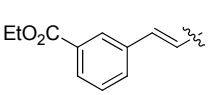
Catalyst System A



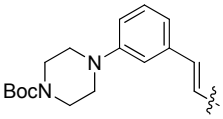
4.5a, 92% (87%)
b/l = 1 : 23



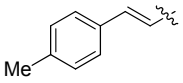
4.5b, 70% (43%)[b]
b/l = 1 : 30



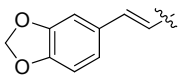
4.5c, 89% (82%)
b/l = 1 : 21



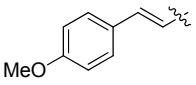
4.5d, 84% (84%)[c]
b/l = 1 : 14



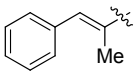
4.5e, 85% (86%)
b/l = 1 : 10



4.5f, 77% (68%)
b/l = 1 : 7

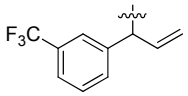


4.5g, 64% (55%)
b/l = 1 : 6

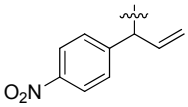


4.5h, 73% (77%)[c]
b/l = 1 : 10

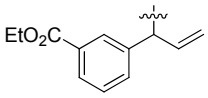
Catalyst System B



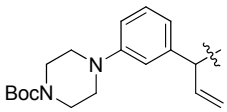
4.6a, 93% (83%)
b/l = 99 : 1



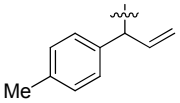
4.6b, 92% (78%)
b/l = 49 : 1



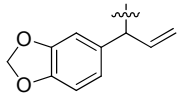
4.6c, 94% (80%)
b/l = 99 : 1



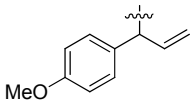
4.6d, 94% (76%)
b/l = 49 : 1



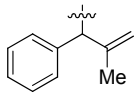
4.6e, 96% (89%)
b/l = 99 : 1



4.6f, 92% (80%)
b/l = 99 : 1



4.6g, 81% (70%)
b/l = 99 : 1

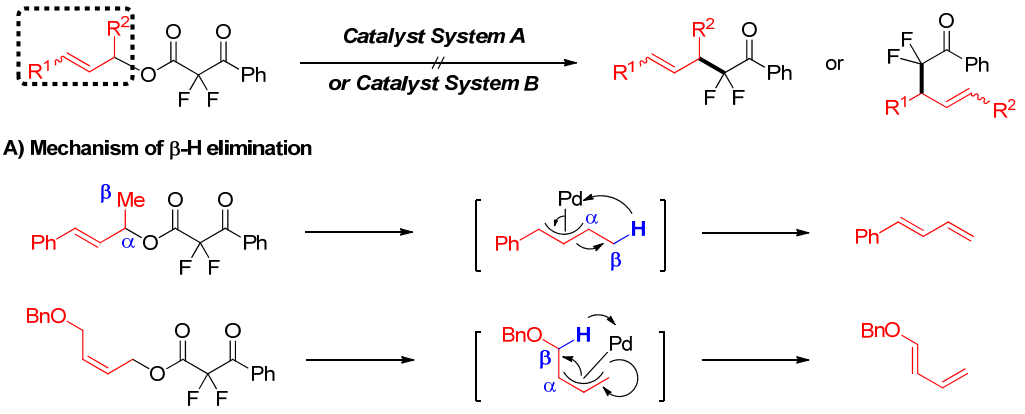


4.6h, 91% (82%)
b/l = 28 : 1

[a] Catalyst System A: **4.4a**–**h** (1.0 equiv), $Pd(OAc)_2$ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: **4.4a**–**h** (1.0 equiv), $Pd(OAc)_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. ^{19}F NMR yields for the major isomers were determined using $PhCF_3$ as an internal standard (average of two runs). The values in parenthe-ses represent the yields of the major products. The regioselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures. [b] 70 °C. [c] $Pd(OAc)_2$ (5 mol%), *t*-BuBrettPhos (10 mol%).

However, substrates bearing β-hydrogens on the allyl fragment underwent β-H elimination (Scheme 4.11A) to generate dienes instead of coupling products. Non-cinnamyl substrates provided either no linear products or low yields of branched products. In these cases, α,α-difluoracetophenone was the major product under the present conditions (Scheme 4.11B).

Scheme 4.11. Substrates that Did Not Provide Coupling Products or Gave Poor Results[a,b]

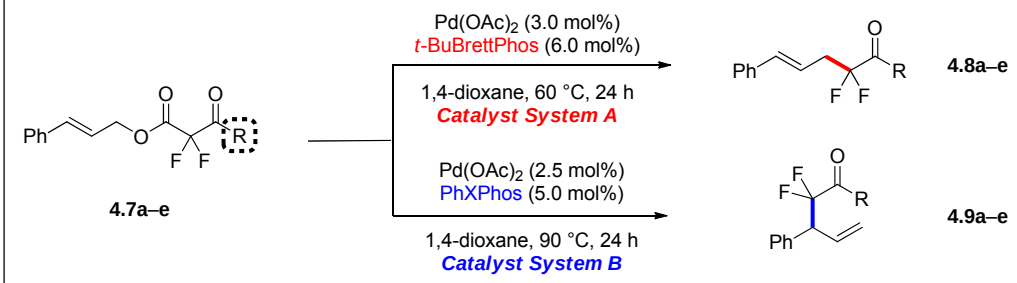


- either no linear products or low yields of branched products (< 23%)
- formation of dienes instead of coupling products
- $PhCOCF_2H$ as the major product

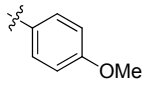
[a] Catalyst System A: substrate (1.0 equiv), $Pd(OAc)_2$ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: substrate (1.0 equiv), $Pd(OAc)_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. The reactions were evaluated by ^{19}F NMR with $PhCF_3$ as an internal standard and by GC-mass. [b] The diene, buta-1,3-dien-1-ylbenzene, was determined by GC-mass.

Both catalyst systems also transformed substrates bearing distinct aryl and alkyl α,α-difluoroketone moieties (Scheme 4.12). Reactions of electron-rich and neutral aryl α,α-difluoroketone substrates afforded good selectivities and yields for the linear **4.8a**–**b** and branched **4.9a**–**b** products under the respective conditions. Even heteroaryl α,α-difluoroketone substrates **4.7c**–**d** generated linear **4.8c**–**d** and branched **4.9c**–**d** products in good selectivities and yields. Under the standard reaction conditions, an aliphatic α,α-difluoroketone was less reactive; however, improved yields and high selectivities were obtained by increasing the catalyst loading [5 mol% $Pd(OAc)_2$, 10 mol% ligands] and reaction time **4.8e** and **4.9e**. Thus, both catalyst systems enabled access to a variety of unique α,α-difluoroketone products, which would be challenging to prepare otherwise.

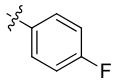
Scheme 4.12. Decarboxylative Difluoroallylation of Substrates Bearing Distinct Ketone Moieties[a]



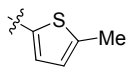
Catalyst System A



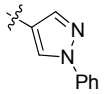
4.8a, 87% (78%)[b]
b/l = 1 : 25



4.8b, 87% (86%)
b/l = 1 : 13



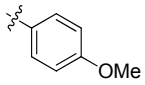
4.8c, 92% (86%)
b/l = 1 : 15



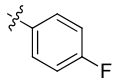
4.8d, 79% (63%)[b]
b/l = 1 : 13

4.8e, 62% (60)[b,c]
b/l = 1 : 20

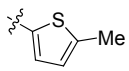
Catalyst System B



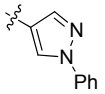
4.9a, 93% (83%)[d]
b/l = 49 : 1



4.9b, 94% (83%)
b/l = 99 : 1



4.9c, 94% (86%)[e]
b/l = 49 : 1



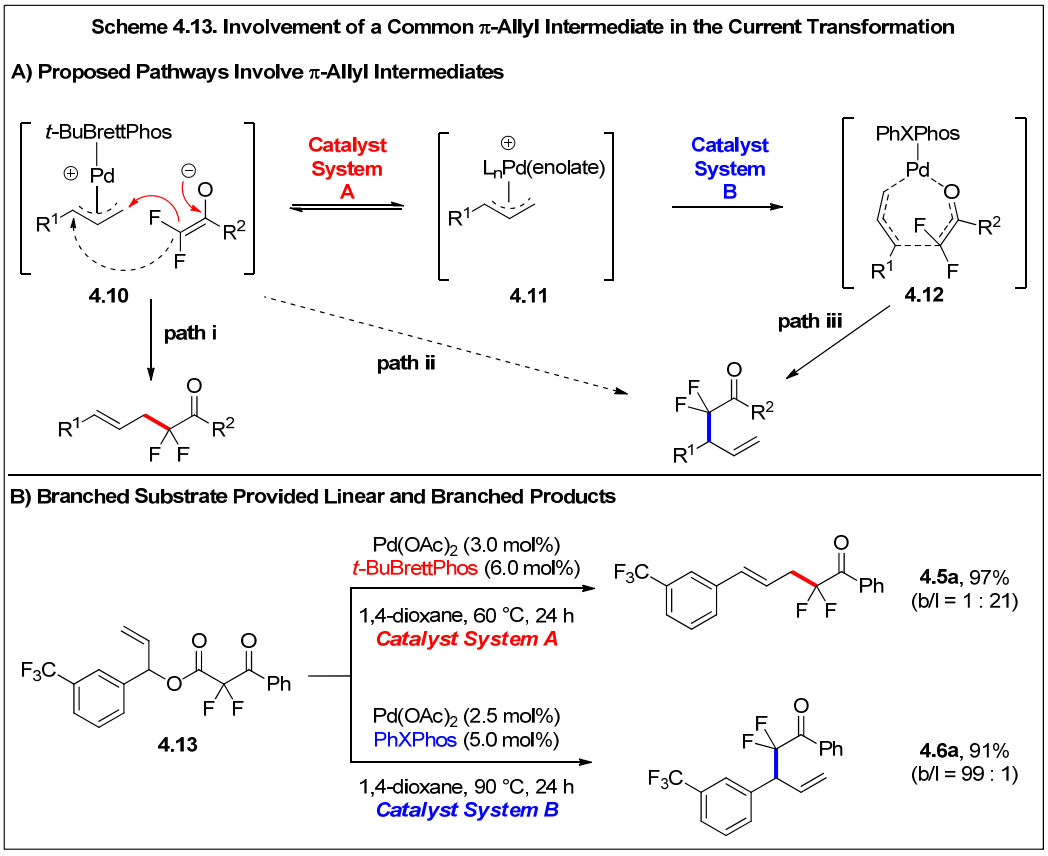
4.9d, 94% (71%)[f]
b/l = 99 : 1

4.9e, 83% (71%)[f,g]
b/l = 63 : 1

[a] Catalyst System A: **4.7a**–**e** (1.0 equiv), $Pd(OAc)_2$ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: **4.7a**–**e** (1.0 equiv), $Pd(OAc)_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. ^{19}F NMR yields for the major isomers were determined by using $PhCF_3$ as an internal standard (average of two runs). The values in parenthe-ses represent the yields of the major products. The regioselectivities were determined by ^1H NMR analysis of the crude reaction mixtures. [b] $Pd(OAc)_2$ (5.0 mol%), *t*-BuBrettPhos (10 mol%). [c] 70 °C, 36 h. [d] $Pd(OAc)_2$ (3.5 mol%), PhXPhos (7.0 mol%). [e] 18 h. [f] $Pd(OAc)_2$ (5.0 mol%), PhXPhos (10 mol%). [g] 90 °C, 36 h.

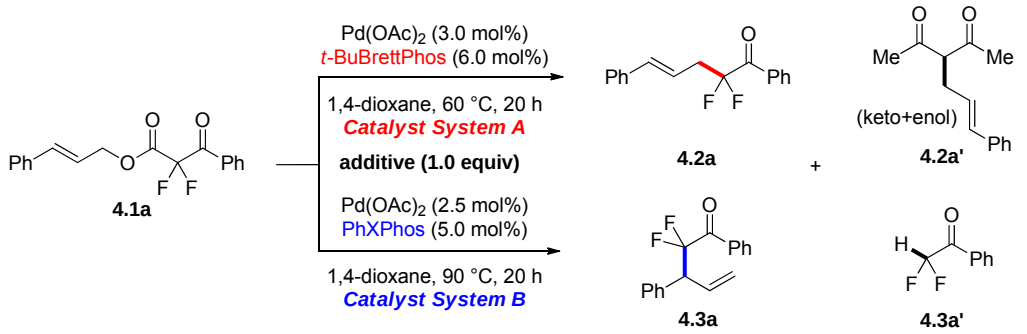
The complementary products may derive from a common L_n–Pd(π-allyl)(enolate) intermediate **4.11** through distinct ligand-controlled regioselective C–C bond-forming events (Scheme 4.13A). To establish the intermediacy of a π-allyl complex, secondary ester **4.13** was subjected to both conditions A and B (Scheme 4.13B), and the results were compared to reactions of the corresponding linear substrate **4.4a** in Scheme 4.11. System A transformed both linear and branched substrates **4.4a** and **4.13** into linear product **4.5a** with comparable selectivity (b/l = 1 : 23 vs. 1 : 21), while system B transformed both linear and branched substrates **4.4a** and **4.13** into branched product **4.6a** with high selectivity (b/l = 99 : 1). Combined, these data 1) implicate the intermediacy of π-allyl species **4.11** in both reaction pathways; 2) discount memory effects controlling the regioselecivity for either system; and 3) confirm that the ligands ultimately control the regiochemical fate of the reaction.

Scheme 4.13. Involvement of a Common π-Allyl Intermediate in the Current Transformation



Subsequent reactions probed the extent of association and/or solvent separation of the α,α-difluoroketone enolate with the palladium π-allyl complex. If free enolate existed in solution, it would be protonated upon addition of an acidic additive. The conjugate base of the additive would then react with the π-allyl complex and regenerate Pd(0) to continue the catalytic cycle. When **4.1a** was subjected to the standard reaction conditions A and B in the presence of 1.0 equivalent of pentane-2,4-dione (acetylacetone; **acac**; pK_a = 13.3 in DMSO), distinct yields of fluorinated products **4.2a**, **4.3a**, alkylated product **4.2a′**, and protonated difluoroketone **4.3a′** were detected (Table 4.2). Catalyst system A provided product **4.2a** in 28% yield, and products **4.2a′** and **4.3a′** in ca. 66% yield (entry 2, Table 4.2). Alternatively, catalyst system B generated **4.3a** in 67% yield, and **4.2a′** and **4.3a′** in lower yields (30% and 32%, respectively, entry 4, Table 4.2). Since formation of products **4.2a′** and **4.3a′** derive from dissociation of the Pd-bound difluoroenolate, the lower yields of **4.2a′** and **4.3a′** generated in the reactions of catalyst system B, which provides the branched product, indicate that the enolate is more tightly associated with the palladium π-allyl complex.

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



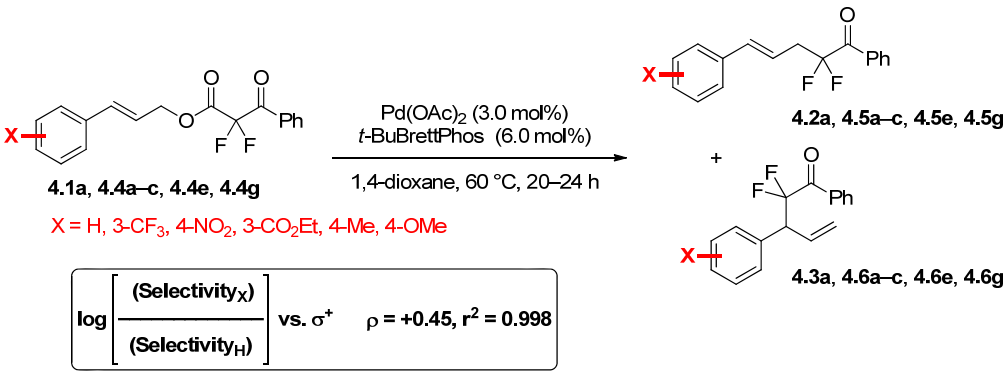
entry	catalyst system[a]	additive	**4.2a** (%)[b]	**4.3a** (%)[b]	**4.2a'** (%)[c]	**4.3a'** (%)[b]	b/l[d]
1	**A**	none	89	4	0	0	1 : 22
2	**A**	**acac**	28	1	66	66	1 : 28
3	**B**	none	1	94	0	0	94 : 1
4	**B**	**acac**	<1	67	30	32	>98 : 2

[a] Catalyst system A: **4.1a** (1.0 equiv, 0.50 M solution in 1,4-dioxane), $Pd(OAc)_2$ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 60 °C, 20 h. Catalyst system B: **4.1a** (1.0 equiv, 0.10 M solution in 1,4-dioxane), $Pd(OAc)_2$ (2.5 mol%), PhXPhos (5.0 mol%), 90 °C, 20 h. [b] Yields were determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [c] The yield of non-fluorinated product was determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [d] The selectivity for branched to linear products was the ratio of **4.3a** to **4.2a**.

Thus, we hypothesized that cinnamyl α,α-difluoro-β-keto esters underwent decarboxylative difluoromethylation to generate linear and branched products *via* different pathways under both catalyst systems. The linear product may come from outer sphere attack of the enolate on less hindered terminus of the π-allyl complex (path i, Scheme 4.13) while the branched product may result from the rearrangement of a seven-membered ring transition state composed of enolate-Pd-π-allyl complex (path iii, Scheme 4.13) as proposed by Stoltz, Goddard III, and Echavarren.[24]

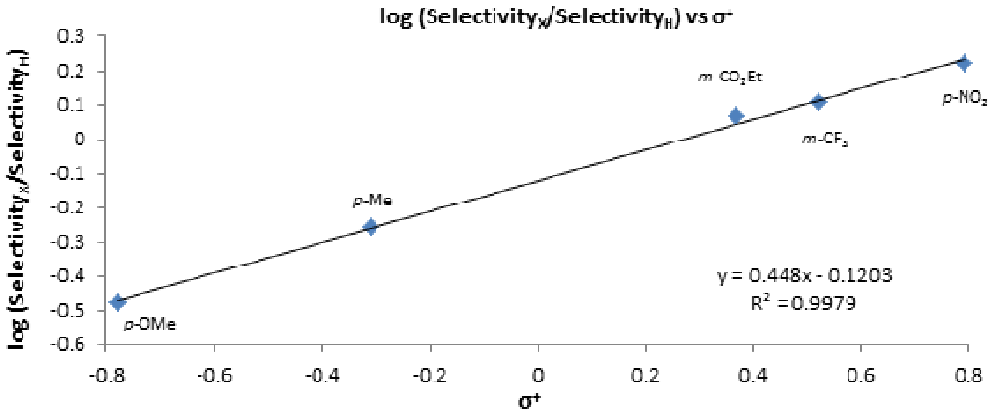
An evaluation of the relationship between the electronic structures of the cinnamyl-derived substrates and the regioselectivities of the catalytic reactions suggests that the branched and linear products derive from distinct pathways. For outer-sphere processes, the electronic structure of the cinnamyl-derived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

Figure 4.1. Catalyst System A Improved Linear Selectivity for Electron-Deficient Substrates



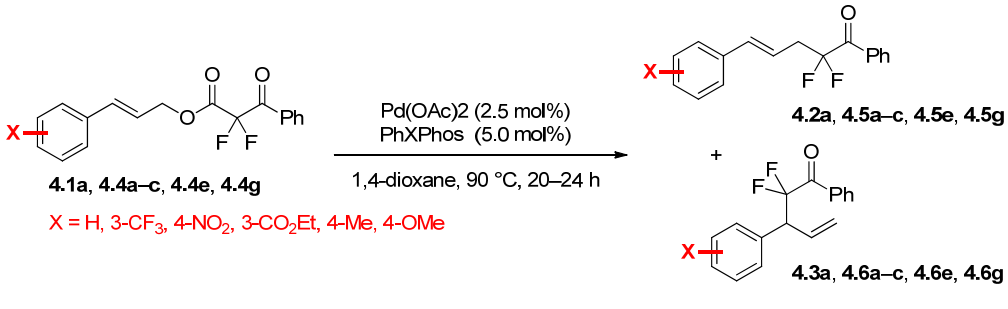
X = H, 3-CF_3, 4-NO_2, 3-CO_2Et, 4-Me, 4-OMe

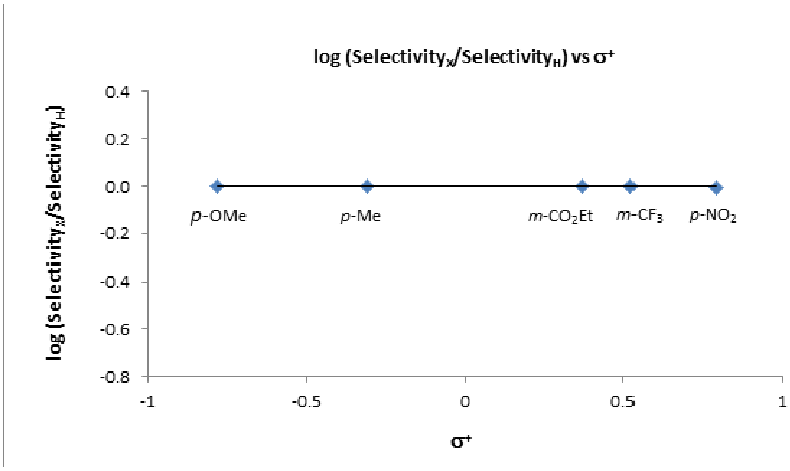
$$\log\left[\frac{(\text{Selectivity}_X)}{(\text{Selectivity}_H)}\right] \text{ vs. } \sigma^+ \qquad \rho = +0.45,\ r^2 = 0.998$$



In contrast, system B notably generates branched products, which are less commonly observed in Pd-catalyzed allylation reactions of hard ketone enolates.[1b,3c,8] If S_N1-like attack of intermediate **4.10** predominantly occurred at the secondary position (path ii, Scheme 4.13), the electronic properties of the cinnamyl-derived substrates **4.1a**, **4.4a–c**, **4.4e** and **4.4g** would likely allow path i to compete and influence the regioselectivity of the reactions.[7b,25] However for system B, substrates bearing electron-rich, -neutral, and -deficient cinnamyl moieties all underwent coupling to afford the branched products in high selectivities **4.3a**, **4.6a–c**, **4.6e** and **4.6g** (Figure 4.2). This lack of a correlation between the electronic properties of the cinnamyl-derived substrates and the regioselectivity may discount the outer-sphere path i.

Figure 4.2. Catalyst System B Showed Non-Correlation between Electronic Characters of Substrates and Branched Selectivity





An alternate explanation for the unique regioselectivity involves the sigmatropic rearrangement of an η^1-allyl intermediate (path iii, Scheme 4.13).[24] Although this mechanism has been computationally predicted, experimental evidence for palladacyclic transition state **4.12** has not been established. In support of this rearrangement mechanism, non-metal-catalyzed 3,3′-sigmatropic rearrangements of allyl α,α-difluoroenol ethers similarly proceed more rapidly than those of the non-fluorinated counterparts.[13a, 26] Thus, in the present case, the fluorine atoms might also provide unique physical properties that facilitate an analogous Pd-catalyzed rearrangement to provide the branched product.

4.5 Conclusion

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

[1] (a) Rodríguez, N.; Goossen, L. J. "Decarboxylative Coupling Reactions: A Modern Strategy for C–C Bond Formation" *Chem. Soc. Rev*. **2011**, *40*, 5030–5048. (b) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. "Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions" *Chem. Rev*. **2011**, *111*, 1846–1913. (c) Behenna, D. C.; Stoltz, B. M. "Natural Products as Inspiration for Reaction Development. Catalytic Enantioselective Decarboxylative Reactions of Prochiral Enolate Equivalents" *Top. Organomet. Chem*. **2013**, *44*, 281–314. (d) Arseniyadis, S.; Fournier, J.; Thangavelu, S.; Lozano, O.; Prevost, S.; Archambeau, A.; Menozzi, C.; Cossy, J. "Palladium-Catalyzed Allylic Alkylation of Allyl Dienol Carbonates. Reactivity, Regioselectivity, Enantioselectivity, and Synthetic Applications" *Synlett* **2013**, *24*, 2350–2364.

[2] (a) Recio III, A.; Tunge, J. A. "Regiospecific Decarboxylative Allylation of Nitriles" *Org. Lett*. **2009**, *11*, 5630–5633. (b) Jana, R.; Partridge, J. J.; Tunge, J. A. "Migratory Decarboxylative Coupling of Coumarins: Synthetic and Mechanistic Aspects" *Angew. Chem. Int. Ed*. **2011**, *50*, 5157–5161.

[3] (a) Lu, Z.; Ma, S. "Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis" *Angew. Chem. Int. Ed*. **2008**, *47*, 258–297. (b) Ding, C.-H.; Hou, X.-L. "Transition Metal-Catalyzed Asymmetric Allylation" *Top. Organomet. Chem*. **2011**, *36*, 247–286. (c) Oliver, S.; Evans, P. A. "Transition-Metal-Catalyzed Allylic Substitution Reactions: Stereoselective Construction of α- and β-Substituted Carbonyl Compounds" *Synthesis* **2013**, *45*, 3179–3198.

[4] (a) Trost, B. M.; Crawley, M. L. "Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis" *Chem. Rev*. **2003**, *103*, 2921–2943. (b) Trost, B. M.; Crawley, M. L. "Enantioselective Allylic Substitutions in Natural Product Synthesis" *Top. Organomet. Chem*. **2011**, *38*, 321–340. (c) Hong, A. Y.; Stoltz, B. M. "The Construction of All-Carbon Quaternary Stereocenters by Use of Pd-Catalyzed Asymmetric Allylic Alkylation Reactions in Total Synthesis" *Eur. J. Org. Chem*. **2013**, 2745–2759.

[5] Hartwig, J. F. *Organotransition Metal Chemistry from Bonding to Catalysis*, University Science Books, California, **2009**, Chap. 20, pp. 967–1014.

[6] (a) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. "Allylic Alkylation: Nucleophilic Attack on π-Allylpalladium Complexes" *J. Am. Chem. Soc*. **1978**, *100*, 3416–3426. (b) Kawatsura, M.; Uozumi, Y.; Hayashi, T. "Regiocontrol in Palladium-Catalyzed Allylic Alkylation by Addition of Lithium Iodide" *Chem. Commun*. **1998**, 217–218. (c) Trost, B. M.; Ariza, X. "Enantioselective Allylations of Azlactones with Unsymmetrical Acyclic Allyl Esters" *J. Am. Chem. Soc*. **1999**, *121*, 10727–10737. (d) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. "Bulky Monodentate Phosphoramidites in Palladium-Catalyzed Allylic Alkylation Reactions: Aspects of Regioselectivity and Enantioselectivity" *Chem. Eur. J*. **2004**, *10*, 6232–6246. (e) Weaver, J. D.; Ka, B. J.; Morris, D. K.; Thompson, W.; Tunge, J. A. "Stereospecific Decarboxylative Allylation of Sulfones" *J. Am. Chem. Soc*. **2010**, *132*, 12179–12181.

[7] (a) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. "Asymmetric Allylic Amination Catalyzed by Chiral Ferrocenylphosphine Palladium Complexes" *Tetrahedron Lett*. **1990**, *31*, 1743–1746. (b) Prétôt, R.; Pfaltz, A. "New Ligands for Regio- and Enantiocontrol in Pd-Catalyzed Allylic Alkylations" *Angew. Chem. Int. Ed*. **1998**, *37*, 323–325. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. "Highly Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation and Amination of Monosubstituted Allylic Acetates with Novel Ferrocene *P*,*N*-Ligands" *J. Am. Chem. Soc*. **2001**, *123*, 7471–7472. (d) Johns, A. M.; Liu, Z.; Hartwig, J. F. "Primary *tert*- and *sec*-Allylamines *via* Palladium-Catalyzed Hydroamination and Allylic Substitution with Hydrazine and Hydroxylamine Derivatives" *Angew. Chem. Int. Ed*. **2007**, *46*, 7259–7261. (e) Fang, P.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. "Palladium-Catalyzed Regio- and Enantio-Selective Allylic Substitution Reaction of Monosubstituted Allyl Substrates with Benzyl Alcohols" *Tetrahedron: Asymmetry* **2010**, *21*, 1176–1178. (f) Zheng, B.-H.; Ding, C.-H.; Hou, X.-L. "Regio- and Enantioselective Pd-Catalyzed Allylic Amination of Monosubstituted Allylic Substrates with BocNHOMe" *Synlett* **2011**, 2262–2264. (g) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. "Achieving

Control over the Branched/Linear Selectivity in Palladium-Catalyzed Allylic Amination" *J. Org. Chem.* **2013**, *78*, 1559–1575. (h) Yang, X.-F.; Yu, W.-H.; Ding, C.-H.; Ding, Q.-P.; Wan, S.-L.; Hou, X.-L.; Dai, L.-X.; Wang, P.-J. "Palladium-Catalyzed Regio-, Diastereo-, and Enantioselective Allylation of Nitroalkanes with Monosubstituted Allylic Substrates" *J. Org. Chem.* **2013**, *78*, 6503–6509.

[8] (a) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. "Selective Carbon-Carbon Bond Formation *via* Transition Metal Catalysis. 29. A Highly Regio- and Stereospecific Palladium-Catalyzed Allylation of Enolates Derived from Ketones" *J. Org. Chem.* **1982**, *47*, 3188–3190. (b) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. "Palladium-Catalyzed Decarboxylation-Allylation of Allylic Esters of α-Substituted β-Keto Carboxylic, Malonic, Cyanoacetic, and Nitroacetic Acids" *J. Org. Chem.* **1987**, *52*, 2988–2995. (c) Trost, B. M.; Schroeder, G. M. "Palladium-Catalyzed Asymmetric Alkylation of Ketone Enolates" *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760. (d) Trost, B. M.; Schroeder, G. M. "Palladium-Catalyzed Asymmetric Allylic Alkylation of Ketone Enolates" *Chem. Eur. J.* **2005**, *11*, 174–184. (e) Trost, B. M.; Xu, J.; Schmidt, T. "Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Enol Carbonates" *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

[9] (a) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. "Highly Regio-, Diastereo-, and Enantioselective Pd-Catalyzed Allylic Alkylation of Acyclic Ketone Enolates with Monosubstituted Allyl Substrates" *J. Am. Chem. Soc.* **2007**, *129*, 7718–7719. Another example for branched products using imines followed by acidic hydrolysis of the products, see (b) Chen, J.-P.; Peng, Q.; Lei, B.-L.; Hou, X.-L.; Wu, Y.-D. "Chemo- and Regioselectivity-Tunable Pd-Catalyzed Allylic Alkylation of Imines" *J. Am. Chem. Soc.* **2011**, *133*, 14180–14183.

[10] Bai, D.-C.; Yu, F.-L.; Wang, W.-Y.; Chen, D.; Li, H.; Liu, Q.-R.; Ding, C.-H.; Chen, B.; Hou, X.-L. "Palladium/*N*-Heterocyclic Carbene Catalysed Regio and Diastereoselective Reaction of Ketones with Allyl Reagents *via* Inner-Sphere Mechanism" *Nature Communications* **2016**, *7*, 11806pp.

[11] (a) Lefebvre, O.; Brigaud, T.; Portella, C. "Mixed Organofluorine-Organosilicon Chemistry. 13. One-Pot Synthesis of Difluoroaldols from Acylsilanes and Trifluoromethyltrimethylsilane. Application to the Synthesis of a Difluoro Analogue of Egomaketone" *J. Org. Chem.* **2001**, *66*, 1941–1946. (b) Wu, L. "A Facile Tandem Reaction to Access β-Hydroxy-α,α-difluoroketone Derivatives Catalyzed by Titanocene Dichloride/Magnesium" *J. Fluorine Chem.* **2011**, *132*, 367–372. (c) Han, C.; Kim, E. H.; Colby, D. A. "Cleavage of Carbon-Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of α,α-Difluoroenolates for Aldol Reactions" *J. Am. Chem. Soc.* **2011**, *133*, 5802–5805. (d) Xie, C.; Wu, L.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. "Synthesis of α,α-Difluoro-β-amino Carbonyl-Containing Sulfonamides and Related Compounds" *J. Fluorine Chem.* **2015**, *172*, 13–21.

[12] (a) Kuroboshi, M.; Ishihara, T. "An Efficient and General Method for the Reformatsky-Type Reaction of Chlorodifluoromethyl Ketones with Carbonyl Compounds Giving α,α-Difluoro-β-hydroxy Ketones" *Bull. Chem. Soc. Jpn.* **1990**, *63*, 428–437. (b) Chung, W. J.; Higashiya, S.; Welch, J. T. "The Indium-Mediated Reformatsky Reactions of 2,2-Difluoro-2-halo-1-furan-2-ylethanones in Aqueous Media" *J. Fluorine Chem.* **2001**, *112*, 343–347. (c) Cao, C.-R.; Jiang, M.; Liu, J.-T. "Metal-Mediated Reformatsky Reaction of Bromodifluoromethyl Ketone and Imine" *Eur. J. Org. Chem.* **2015**, 1144–1151.

[13] (a) Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. "The Synthesis of α,α-Difluoroaldehydes and Ketones *via* Claisen Rearrangements" *Tetrahedron Lett.* **1985**, *26*, 2861–2864. (b) Garayt, M. R.; Percy, J. M. "A Direct and Useful Route to Difluoroacylsilanes and Difluoroacylstannanes and Their Potential for the Generation of Structurally Diverse Difluoroketones" *Tetrahedron Lett.* **2001**, *42*, 6377–6380.

[14] (a) Lefebvre, O.; Brigaud, T.; Portella, C. "Mixed Organofluorine-Organosilicon Chemistry. 10. Allylation and Benzylation of Difluoroenoxysilanes. Application to the Synthesis of *gem*-Difluoroterpene Analogues" *Tetrahedron* **1999**, *55*, 7233–7242. (b) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. "A New Finding in Selective Baeyer-Villiger Oxidation of α-Fluorinated Ketones; A New and Practical Route for the Synthesis of α-Fluorinated Esters" *Tetrahedron* **2003**, *59*, 1547–1552.

[15] (a) Ambler, B. R.; Altman, R. A. "Copper-Catalyzed Decarboxylative Trifluoromethylation of Allylic Bromodifluoroacetates" *Org. Lett.* **2013**, *15*, 5578–5581. (b) Ambler, B. R.; Peddi, S.; Altman, R. A.

"Copper-Catalyzed Decarboxylative Trifluoromethylation of Propargyl Bromodifluoroacetates" *Synthesis* **2014**, *46*, 1938–1946. (c) 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*, 7122–7131. (c) Yang, M.-H.; Orsi, D. L.; Altman, R. A. "Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation Reaction to Access α,α-Difluoroketones" *Angew. Chem. Int. Ed.* **2015**, *54*, 2361–2365.

[16] (a) Shimizu, I.; Ishii, H. "Synthesis of α-Fluoroketones Based on Palladium-Catalyzed Decarboxylation Reactions of Allyl β-Keto Carboxylates" *Tetrahedron* **1994**, *50*, 487–495. (b) Shimizu, I.; Ishii, H.; Tasaka, A. "Facile Synthesis of Trifluoromethyl Ketones by Palladium-Catalyzed Carroll-Type Reaction" *Chem. Lett.* **1989**, 1127–1128. (c) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. "Synthesis of Chiral α-Fluoroketones through Catalytic Enantioselective Decarboxylation" *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251. (d) Burger, E. C.; Barron, B. R.; Tunge, J. A. "Catalytic Asymmetric Synthesis of Cyclic α-Allylated α-Fluoroketones" *Synlett* **2006**, 2824–2826.

[17] (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. "A Rationally Designed Universal Catalyst for Suzuki-Miyaura Coupling Processes" *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876. (b) Surry, D. S.; Buchwald, S. L. "Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide" *Chem. Sci.* **2011**, *2*, 27–50.

[18] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. "Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure" *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[19] (a) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. "Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation" *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007. (b) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. "An Efficient System For the Pd-Catalyzed Cross-Coupling of Amides and Aryl Chlorides " *Tetrahedron* **2009**, *65*, 6576–6583.

[20] (a) Trost, B. M.; Van Vranken, D. L. "Asymmetric Transition Metal-Catalyzed Allylic Alkylations" *Chem. Rev.* **1996**, *96*, 395–422. (b) Trost, B. M.; Thaisrivongs, D. A. "Strategy for Employing Unstabilized Nucleophiles in Palladium-Catalyzed Asymmetric Allylic Alkylations" *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093.

[21] Norsikian, S.; Chang, C.-W. "Control of the Regioselectivity in Palladium(0)-Catalyzed Allylic Alkylation" *Advances in Organic Synthesis*, **2013**, *3*, 81–138.

[22] Bordwell, F. G. "Equilibrium Acidities in Dimethyl Sulfoxide Solution" *Acc. Chem. Res.* **1988**, *21*, 456–463.

[23] (a) Ni, C.; Zhang, L.; Hu, J. "Nucleophilic Fluoroalkylation of α,β-Enones, Arynes, and Activated Alkynes with Fluorinated Sulfones: Probing the Hard/Soft Nature of Fluorinated Carbanions" *J. Org. Chem.* **2008**, *73*, 5699–5713. (b) Zhang, W.; Ni, C.; Hu, J. "Selective Fluoroalkylation of Organic Compounds by Tackling the "Negative Fluorine Effect" *Top. Curr. Chem.* **2012**, *308*, 25–44.

[24] (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard III, W. A. "The Inner-Sphere Process in the Enantioselective Tsuji Allylation Reaction with (*S*)-*t*-Bu-phosphinooxazoline Ligands" *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877. (b) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard III, W. A. "The Reaction Mechanism of the Enantioselective Tsuji Allylation: Inner-Sphere and Outer-Sphere Pathways, Internal Rearrangements, and Asymmetric C–C Bond Formation" *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060. (c) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. "Intramolecular Coupling of Allyl Carboxylates with Allyl Stannanes and Allyl Silanes: A New Type of Reductive Elimination Reaction?" *Chem. Eur. J.* **2002**, *8*, 3620–3628.

[25] Hayashi, T.; Kawatsura, M.; Uozumi, Y. "Regioselective and Enantioselective Allylic Alkylation Catalyzed by a Chiral Monophosphine-Palladium Complex" *Chem. Commun.* **1997**, 561–562.

[26] Cresson, I. P. "Application of the Claisen Rearrangement in the Synthesis of γ,δ-Ethylenic Aldehydes" *Bull. Soc. Chim. Fr.* **1964**, 2618–2628.

Chapter 4 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 4

Table of Contents

General Information

Unless otherwise noted, reactions were performed under an atmosphere of N_2 using oven-dried glassware. Palladium-catalyzed reactions were performed in 1 dram vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with $KMnO_4$ or nihydrin. Column chromatography was conducted using an automated system. ^{19}F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. 1,4-Dioxane (anhydrous, 99.8%) and $Pd(OAc)_2$ (reagent grade, 98%) were purchased from Sigma Aldrich. All ligands for screening were purchased from Sigma Aldrich or Strem with the following exceptions: *t*-BuBrettPhos and PhXPhos were prepared according to previously reported syntheses.[1,2] Solvents including DMF, PhMe, CH_2Cl_2, THF, MeOH were used directly from a solvent purification system in which solvent was dried by passage through two columns of activated alumina under argon.

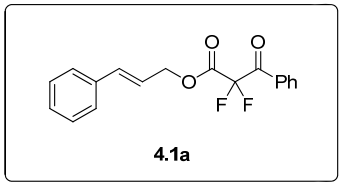
Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual $CHCl_3$ in the NMR solvent ($CHCl_3$: δ = 7.27 ppm or DMSO-d_6: δ = 2.50 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak ($CDCl_3$: δ = 77.23 ppm or DMSO-d_6: δ = 39.51 ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ^{19}F NMR chemical shifts (δ) are reported in ppm upfield from

trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), integration. Gas chromatography (GC) data were obtained via analysis using an Agilent Technologies 7890A GC system with a FID detector and an Agilent Technologies 30 m x 0.320 mm i.d. HP–5 capillary column. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier^{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 at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

Preparation of Known Compounds

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

Preparation of Compound 4.1a



4.1a

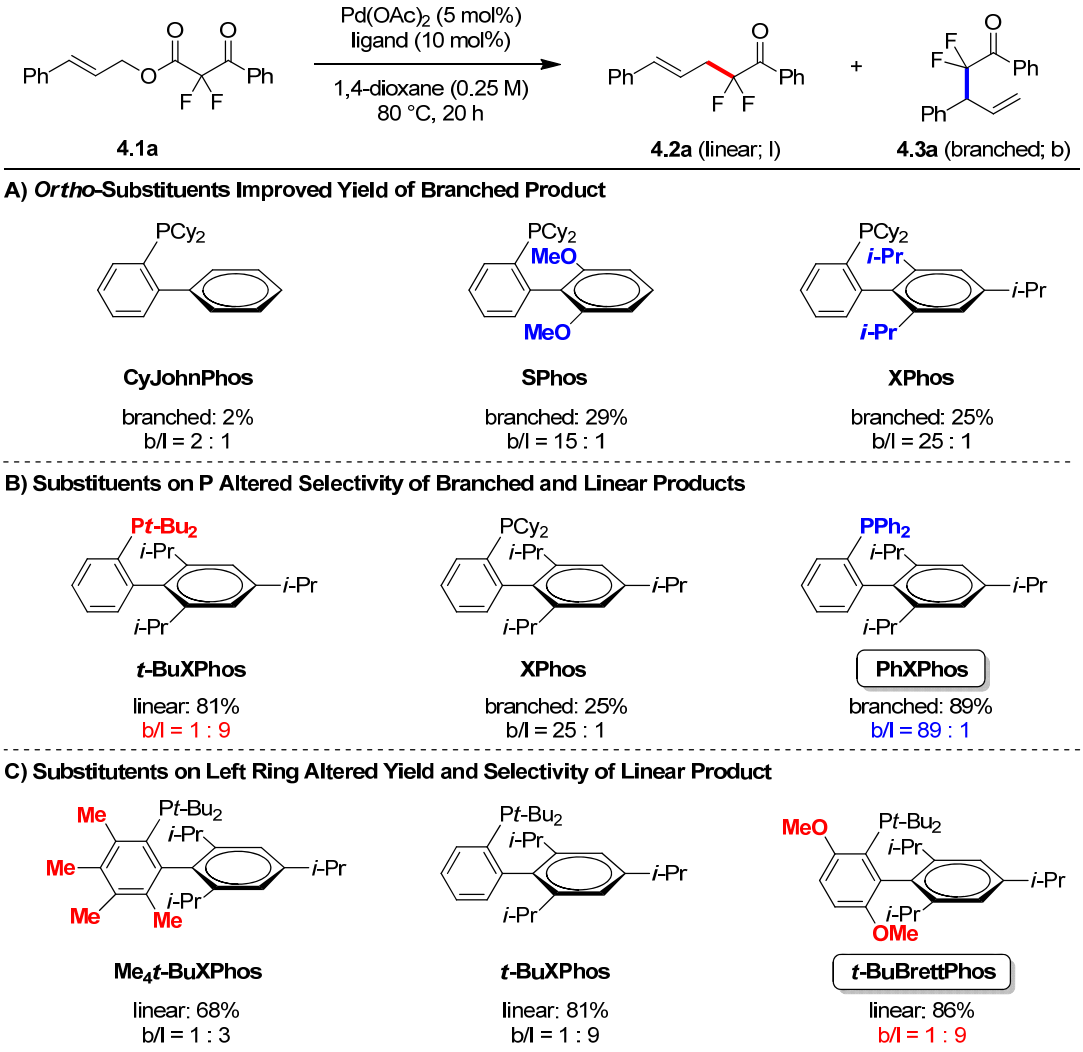
cinnamyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.1a)

An oven-dried one-neck round-bottom flask was charged with Potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (3.00 g, 12.6 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (0.040 L) and DMF (1.2 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (1.2 mL, 14 mmol) was added dropwise, and then the reaction mixture

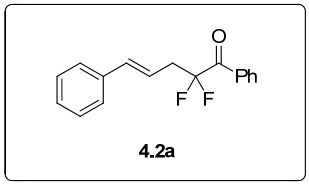
was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol (2.54 g, 18.9 mmol) dissolved in dry CH_2Cl_2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et_3N (2.6 mL, 19 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H_2O (10 mL) was added to quench the reaction, and CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **4.1a** as a as a colorless oil (3.20 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 7.6 Hz, 2 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.38–7.29 (m, 5 H), 6.69 (d, *J* = 15.6 Hz, 1 H), 6.23 (dt, *J* = 16, 6.8 Hz, 1 H), 4.98 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 136.5, 135.8, 135.4, 131.2, 130.2 (t, *J* = 2.5 Hz), 129.2, 128.9, 128.7, 127.0, 120.9, 110.0 (t, *J* = 263.8 Hz), 68.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (s, 2 F). IR (film) 3061, 3028, 1776, 1715, 1699, 1597, 1450, 1312, 1159, 1124, 968, 922, 746, 712, 688 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{14}F_2O_3Na$ $[M+Na]^+$ 339.0809, found 339.0804.

Screening of Ligands

An oven-dried 1 dram vial was charged with substrate **4.1a** (47.4 mg, 0.150 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), ligand (7.0 mg, 0.0150 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, evacuated and backfilled with $N_{2(g)}$ four times. Dry 1,4-dioxane (0.60 mL) was added *via* a syringe under $N_{2(g)}$. The vial was sealed with a screwed-cap under $N_{2(g)}$ flow, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at 80 °C for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (3 mL). Dodecane (0.020 mL, 0.088 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. A small aliquot was taken from the vial, passed through a plug of silica gel, and eluted with additional EtOAc (2 mL). The sample was analyzed using GC/FID, and the quantity of compounds **4.2a** and **4.3a** were determined using dodecane as an internal standard.



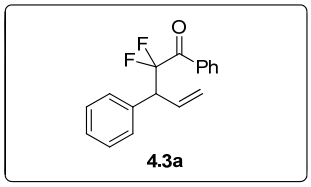
Characterization of Compounds 4.2a and 4.3a



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

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dt, *J* = 8.4, 1.4 Hz, 2 H), 7.65 (tt, *J* = 7.6, 1.4 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 2 H), 7.39–7.36 (m, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.27–7.23 (m, 1 H), 6.60 (d, *J* = 15.6 Hz, 1 H), 6.22 (dt, *J* = 15.6, 7.2 Hz, 1 H), 3.14 (tdd, *J* = 17.2, 7.2, 1.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, *J* = 31.2 Hz), 136.9, 136.4, 134.6, 132.2 (t, *J* = 2.5 Hz), 130.4 (t, *J* = 3.1 Hz), 128.9, 128.8, 128.0,

126.6, 119.0 (t, J = 5.6 Hz), 118.9 (t, J = 253.1 Hz), 38.0 (t, J = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.9 (t, J = 16.9 Hz, 2 F). IR (film) 3059, 3026, 1701, 1597, 1448, 1273, 1173, 1119, 1090, 1061, 966, 947, 914, 748, 716, 688, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{15}F_2O$ $[M+H]^+$ 273.1091, found 273.1092. mp 45–46 °C.

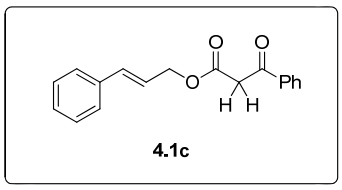


4.3a

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

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (dt, J = 8.8, 1.4 Hz, 2 H), 7.61 (tt, J = 7.6, 1.4 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 2 H), 7.33–7.28 (m, 5 H), 6.22 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.32 (d, J = 10.4 Hz, 1 H), 5.23 (dt, J = 16.8, 1.2 Hz, 1 H), 4.32 (td, J = 16.4, 8.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0 (t, J = 29.4 Hz), 135.3, 134.2, 133.1, 132.6 (t, J = 4.4 Hz), 130.1 (t, J = 3.1 Hz), 129.8, 128.8, 128.0, 120.8, 118.8 (t, J = 257.5 Hz), 54.2 (t, J = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.5 (dd, A of ABX, J_{AB} = 274.5 Hz, J_{AX} = 15.0 Hz, 1 F), –103.1 (dd, B of ABX, J_{AB} = 274.5 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 3065, 3032, 1701, 1597, 1448, 1267, 1178, 1049, 930, 746, 716, 698, 688 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2ONa$ $[M+Na]^+$ 295.0910, found 295.0902.

Preparation of Compounds 4.1b and 4.1c in Table 4.1

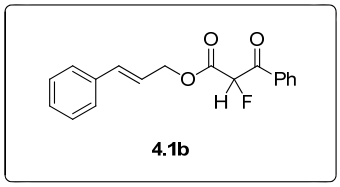


4.1c

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

Compound **4.1c** was prepared according to a previous report.[4] A mixture of cinnamyl alcohol (1.34 g, 10.0 mmol), ethyl benzoylacetate (1.73 g, 10.0 mmol), DMAP (1.22 g, 10.0 mmol) was stirred with oven-dried 4 Å molecular sieves (50 g) in dry toluene (0.080 L) at 100–105 °C for 36 h. The reaction mixture was cooled to rt, and filtered to remove the molecular sieves. The solvents were removed under reduced

pressure, and EtOAc (60 mL) and water (60 mL) were added to the residue. The layers were separated, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **4.1c** as a as a yellow oil (2.08 g, 74%, ketone : enol = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.53 (s, 1 H, enol), 7.98–7.96 (m, 2 H, keto), 7.82–7.79 (m, 2 H, enol), 7.61 (tt, *J* = 7.4, 1.6 Hz, 1 H, keto), 7.51–7.42 (m, 7 H, enol + keto), 7.39–7.25 (m, 8 H, enol + keto), 6.72 (d, *J* = 16.0 Hz, 1 H, enol), 6.64 (d, *J* = 16.0 Hz, 1 H, keto), 6.36 (dt, *J* = 16.0, 6.4 Hz, 1 H, enol), 6.26 (dt, *J* = 16.0, 6.4 Hz, 1 H, keto), 5.74 (s, 1 H, enol), 4.89 (dd, *J* = 6.4, 1.6 Hz, 2 H, enol), 4.83 (dd, *J* = 6.4, 1.6 Hz, 2 H, keto), 4.06 (s, 2 H, keto). HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}O_3Na$ $[M+Na]^+$ 303.0997, found 303.0996. Spectroscopic data matched that from the previous report.[5]



4.1b

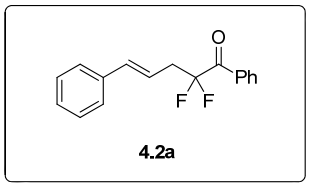
cinnamyl 2-fluoro-3-oxo-3-phenylpropanoate (4.1b)

Compound **4.1b** was prepared according to a previous report.[6] Compound **4.1c** (1.03 g, 3.67 mmol) and $CpTiCl_3$ (39.5 mg, 0.180 mmol) were dissolved in CH_3CN (0.020 L) at rt, and selectfluor (1.40 g, 4.04 mmol) was added. The mixture was stirred at rt for 6 h, and filtered to remove solids. The filtrate was concentrated, and the crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound **4.1b** as a as a colorless oil (0.75 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.64 (tt, *J* = 7.4, 1.4 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.35–7.26 (m, 5 H), 6.62 (dt, *J* = 16.0, 1.4 Hz, 1 H), 6.21 (dt, *J* = 16.0, 6.4 Hz, 1 H), 5.94 (d, *J* = 48.8 Hz, 1 H), 4.90 (dt, *J* = 6.4, 1.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.6 (d, *J* = 20.0 Hz), 164.9 (d, *J* = 23.8 Hz), 135.9, 135.8, 134.7, 133.5 (d, *J* = 2.5 Hz), 129.7 (d, *J* = 3.8 Hz), 129.0, 128.8, 128.5, 126.9, 121.5, 90.2 (d, *J* = 196.2 Hz), 67.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –190.2 (d, *J* = 48.9 Hz, 1

F). IR (film) 1763, 1691, 1597, 1448, 1242, 1198, 1111, 966, 744, 690 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{15}FO_3Na$ $[M+Na]^+$ 321.0903, found 321.0894.

Experimental Procedures and Characterization of Compounds for Table 4.1

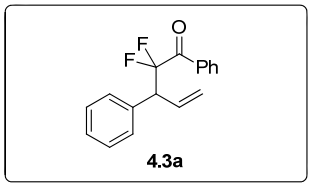
General Procedure A: An oven-dried 1 dram vial was charged with substrate (**4.1a**, **4.1b** or **4.1c**), $Pd(OAc)_2$, ligand (*t*-BuBrettPhos or PhXPhos), and a magnetic stir bar. The vial was equipped with a three-way valve, evacuated and backfilled with $N_{2(g)}$ four times. Dry 1,4-dioxane was added *via* a syringe under $N_{2(g)}$. The vial was sealed with a screwed-cap under $N_{2(g)}$ flow, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at the indicated temperature for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc. An internal standard was added, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing before checking ^{19}F or ^{1}H yields.



4.2a

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

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

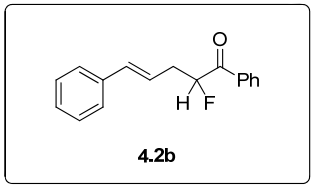


4.3a

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

General procedure A was followed using **4.1a** (84.1 mg, 0.300 mmol), $Pd(OAc)_2$ (1.68 mg, 0.0075 mmol), PhXPhos (6.97 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). α,α,α-trifluorotoluene (15 μL) was added as

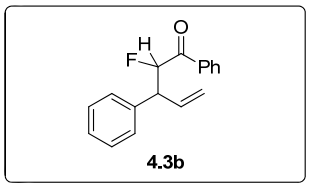
an internal standard to obtain a ^{19}F NMR yield of branched product **4.3a**. Spectral data of **4.3a** matched that described above.



4.2b

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

General procedure A was followed using **4.1b** (89.5 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.0090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Fluorobenzene (15 μL) was added as an internal standard to obtain ^{19}F NMR yields. After determination of the ^{19}F NMR yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. Removal of the solvents and chromatographic purification provided the linear product **4.2b** (15.2 mg, 20%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.0 Hz, 2 H), 7.63 (tt, *J* = 7.4, 1.5 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.39–7.22 (m, 5 H), 6.53 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.27 (dt, *J* = 16.0, 7.2 Hz, 1 H), 5.69 (ddd, *J* = 49.0, 7.4, 4.8 Hz, 1 H), 3.02–2.82 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.4 (d, *J* = 20.0 Hz), 137.0, 134.6, 134.3, 134.1, 129.2 (d, *J* = 3.8 Hz), 129.0, 128.8, 127.8, 126.5, 123.0 (d, *J* = 3.8 Hz), 93.2 (d, *J* = 185.0 Hz), 36.4 (d, *J* = 21.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –187.8 (ddd, J = 48.9, 30.1, 22.5 Hz, 1 F). IR (film) 3026, 2922, 1701, 1597, 1578, 1448, 1228, 1072, 964, 744, 694 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{15}FONa$ $[M+Na]^+$ 277.1005, found 277.0995.

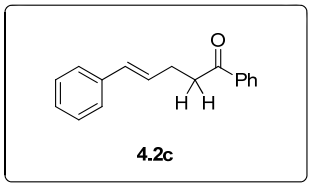


4.3b

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

General procedure A was followed using **4.1b** (89.5 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Fluorobenzene (15 μL) was added as an internal standard to obtain ^{19}F NMR yields. After determination of the ^{19}F yield, the aliquot was

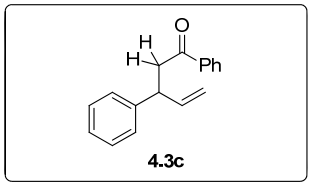
recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. Removal of the solvents and chromatographic purification provided the branched product **4.3b** as two diastereoisomers (16 mg, 21%, A : B = 2.2 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90–7.88 (m, 2 H, isomer A), 7.79 (dt, *J* = 8.4, 1.2 Hz, 2 H, isomer B), 7.62–7.22 (m, 16 H, isomers A and B), 6.19 (ddd, *J* = 17.2, 10.2, 8.2 Hz, 1 H, isomer A), 6.16 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1 H, isomer B), 5.83 (dd, *J* = 48.4, 4.0 Hz, 1 H, isomer A), 5.78 (dd, *J* = 48.8, 5.2, 1 H, isomer B), 5.24–5.18 (m, 1 H for isomer A and 2 H for isomer B), 5.07 (dt, *J* = 17.2, 1.2 Hz, 1 H, isomer A), 4.16–4.01 (m, 4 H, isomers A and B). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.5 (d, *J* = 20.0 Hz, isomer B), 196.0 (d, *J* = 18.7 Hz, isomer A), 139.4 (isomer A), 137.7 (isomer B), 136.1 (d, *J* = 5.0 Hz, isomer B), 135.3 (isomer B), 135.2 (isomer A), 134.3 (d, *J* = 5.0 Hz, isomer A), 133.9 (isomer A), 133.8 (isomer B), 129.1 (isomers A and B), 129.0 (isomers A and B), 128.9 (isomers A and B), 128.8 (isomers A and B), 127.6 (isomers A and B), 119.1 (isomer A), 118.1 (isomer B), 95.9 (d, *J* = 190.0 Hz, isomer B), 95.7 (d, *J* = 191.2 Hz, isomer B), 52.6 (d, *J* = 20.0 Hz, isomer A), 52.3 (d, *J* = 20.0 Hz, isomer B). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –194.9 (dd, *J* = 48.9, 26.3 Hz, 1 F, isomer A), –191.9 (dd, *J* = 48.9, 26.3 Hz, 1 F, isomer B). IR (film) 3063, 2924, 1697, 1691, 1597, 1491, 1448, 1277, 1252, 1095, 926, 756, 698 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{15}FONa$ $[M+Na]^+$ 277.1005, found 277.0999.



4.2c

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

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



4.3c

1,3-diphenylpent-4-en-1-one (4.3c)

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

Experimental Procedures and Characterization of Compounds in Scheme 4.10

General Procedure B: An oven-dried round-bottom flask was charged with cinnamic acid derivative (12 mmol), and dry MeOH (25 mL) was added. The mixture was cooled to 0 °C, and thionyl chloride (24 mmol) was added dropwise. The reaction mixture was warmed to rt, and then stirred at reflux for 6 h. The reaction mixture was cooled to rt, and MeOH and thionyl chloride were removed under reduced pressure. EtOAc (25 mL) and H_2O (10 mL) were added to the residue, and the solution was neutralized with $NaHCO_{3(aq)}$. The phases were separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the desired product without further purification.

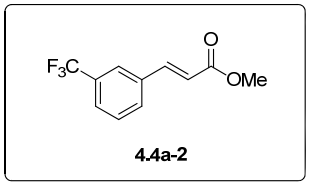
General Procedure C: An oven-dried three-neck flask was charged with cinnamic ester (8.0 mmol). The reaction vessel was equipped with a liquid addition funnel, evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (0.020 L) was added at rt, and then the solution was cooled to –78 °C. DIBAL (1.0 M in hexane, 0.020 L, 0.020 mol) was added dropwise, and then the reaction solution was gradually warmed to rt. The reaction solution was cooled to 0 °C, and 1 N HCl was added dropwise to quench the reaction until no precipitate remained. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the desired product without further purification.

General Procedure D: An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (4.8 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (24 mL) and DMF (1.2 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (4.0 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol derivative (4.0 mmol) dissolved in dry CH_2Cl_2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et_3N (8.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H_2O (10 mL) was added to quench the reaction, and the CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

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

General Procedure F: Pd-Catalyzed Decarboxylation to Generate Branched Difluoroketone Product: An oven-dried 1 dram vial was charged with the substrate **4a–h** (0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075

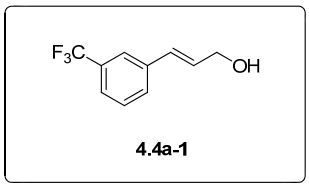
mmol), PhXPhos (7.0 mg, 0.0150 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, and evacuated and backfilled with $N_{2(g)}$ four times. Dry 1,4-dioxane (3.0 mL) was added *via* a syringe under $N_{2(g)}$. The vial was sealed with a screwed-cap under $N_{2(g)}$, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block at 90 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.50 mL). α,α,α-Trifluorotoluene (15 μL, 0.12 mmol) or 2,2,2-trifluoroethanol (0.010 mL, 0.14 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis. After determination of the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. (In some cases, EtOAc was used for elution). Removal of the solvents and chromatographic purification provided the desired product **6a**–**h**.



4.4a-2

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

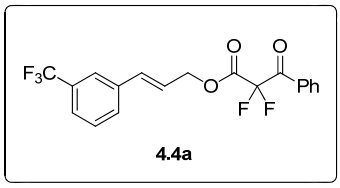
General procedure B was followed using 3-(trifluoromethyl)cinnamic acid (1.50 g, 6.94 mmol), thionyl chloride (1.0 mL, 14 mmol), and MeOH (15 mL). Workup afforded the title compound **4.4a-2** as a colorless solid (1.52 g, 95%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77–7.69 (m, 3 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 1 H), 6.52 (d, J = 16.0 Hz, 1 H), 3.84 (s, 3 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –62.9 (s, 3 F). HRMS (ESI, *m/z*): calcd for $C_{11}H_{10}F_3O_2$ $[M+H]^+$ 231.0633, found 231.0641. Spectroscopic data matched that from the previous report.[9]



4.4a-1

(*E*)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol (4.4a-1)

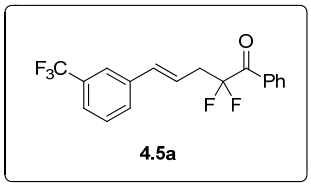
General procedure C was followed using **4.4a-2** (1.38 g, 6.00 mmol), DIBAL (1.0 M in hexane, 15 mL, 15 mmol), and CH_2Cl_2 (15 mL). Workup afforded the title compound **4.4a-1** as a light yellow oil (1.15 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1 H), 7.57–7.54 (m, 1 H), 7.51–7.49 (m, 1 H), 7.46–7.42 (m, 1 H), 6.67 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.45 (dt, *J* = 16.0, 5.4 Hz, 1 H), 4.37 (dd, *J* = 5.4, 1.6 Hz, 2 H), 1.63 (s, 3 H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –62.8 (s, 3 F). HRMS (ESI, *m/z*): calcd for $C_{10}H_{10}F_3O$ $[M+H]^+$ 203.0684, found 203.0674. Spectroscopic data matched that from the previous report.[9]



4.4a

(*E*)-3-(3-(trifluoromethyl)phenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4a)

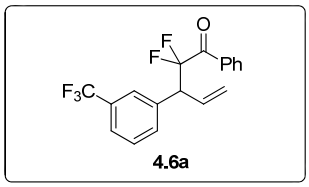
General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), **4.4a-1** (0.81 g, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), DMF (1.2 mL), and CH_2Cl_2 (24 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.4a** as a colorless oil (1.2 g, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, *J* = 8.0 Hz, 2 H), 7.69–7.66 (m, 1 H), 7.58–7.51 (m, 5 H), 7.48–7.45 (m, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.30 (dtd, *J* = 10.0, 6.0, 1.5 Hz, 1 H), 5.00 (d, *J* = 6.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5 (t, *J* = 27.5 Hz), 161.8 (t, *J* = 30.6 Hz), 136.6, 135.4, 134.5, 131.3 (q, *J* = 32.5 Hz), 131.1, 130.2 (t, *J* = 2.5 Hz), 130.1, 129.4, 129.2, 124.2 (q, *J* = 271.3 Hz), 125.2 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 3.8 Hz), 123.0, 110.1 (t, *J* = 263.8 Hz), 67.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F), –62.8 (s, 3 F). IR (film) 3067, 2960, 1778, 1715, 1699, 1599, 1450, 1336, 1312, 1165, 1124, 1097, 966, 924, 793, 712, 696, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{13}F_5O_3Na$ $[M+Na]^+$ 407.0683, found 407.0611.



4.5a

(*E*)-2,2-difluoro-1-phenyl-5-(3-(trifluoromethyl)phenyl)pent-4-en-1-one (4.5a)

General procedure E was followed using **4.4a** (115.3 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.5a** as a colorless oil (90.4 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, *J* = 8.2, 1.4, 2 H), 7.70–7.65 (m, 1 H), 7.62 (s, 1 H), 7.57–7.51 (m, 4 H), 7.47–7.43 (m, 1 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.32 (dt, *J* = 16.0, 7.2 Hz, 1 H), 3.18 (tdd, *J* = 16.8, 7.2, 1.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (t, *J* = 31.3 Hz), 137.6, 135.0, 134.7, 132.0 (t, *J* = 2.5 Hz), 131.2 (q, *J* = 32.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.7, 129.2, 129.0, 124.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.3 Hz), 123.3 (q, *J* = 3.8 Hz), 121.3 (t, *J* = 5.0 Hz), 118.8 (t, *J* = 253.1 Hz), 37.9 (t, *J* = 23.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.7 (t, *J* = 16.9 Hz, 2 F), –62.8 (s, 3 F). IR (film) 3065, 1701, 1599, 1450, 1331, 1169, 1124, 1072, 966, 798, 716, 696 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{18}H_{14}F_5O$ $[M+H]^+$ 341.0965, found 341.0951.

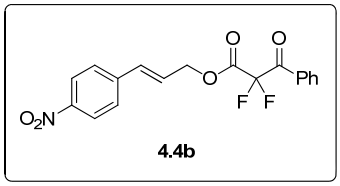


4.6a

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

General procedure F was followed using **4.4a** (115 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.6a** as a colorless oil (86.5 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (dd, *J* = 8.6, 1.0 Hz, 2 H), 7.66–7.61 (m, 1 H), 7.59–7.55 (m, 3 H), 7.51–7.44 (m, 3 H), 6.20 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1 H), 5.36 (dd, *J* = 10.2, 1.0 Hz, 1 H), 5.24 (d, *J* = 16.8 Hz, 1 H), 4.42 (ddd, *J* = 17.4, 14.6, 8.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, *J* = 29.4 Hz), 136.5, 134.5, 133.3, 132.8 (t, *J* = 2.5 Hz), 131.9 (t, *J* = 3.8 Hz), 131.1 (q, *J* = 31.9 Hz), 130.1 (t, *J* = 3.8 Hz), 129.3, 128.9, 126.7 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 270.0 Hz), 121.6, 118.5 (t, *J* = 257.5 Hz), 53.6 (t, *J* = 21.3 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.7 (dd, A of ABX, J_{AB} = 280.1 Hz, J_{AX} = 16.9 Hz, 1 F), –102.2 (dd, B of ABX, J_{AB} = 280.1 Hz, J_{BX} = 15.0 Hz, 1 F), –62.6 (s, 3 F). IR (film)

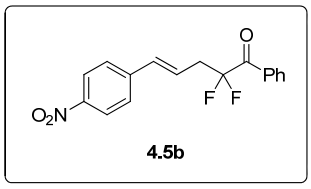
3076, 1705, 1599, 1450, 1331, 1169, 1128, 1076, 926, 795, 716, 702, 688 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{18}H_{14}F_5O$ $[M+H]^+$ 341.0965, found 341.0971.



4.4b

(*E*)-3-(4-nitrophenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4b)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.4 g, 5.5 mmol), oxalyl chloride (0.36 mL, 4.2 mmol), 4-nitrocinnamyl alcohol (0.75 g, 4.2 mmol), Et_3N (1.2 mL, 8.4 mmol), DMF (1.2 mL), and CH_2Cl_2 (0.040 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **4.4b** as a pale yellow solid (1.2 g, 79%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, *J* = 8.8 Hz, 2 H), 8.11 (d, *J* = 7.6 Hz, 2 H), 7.72–7.67 (m, 1 H), 7.56–7.50 (m, 4 H), 6.75 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.41 (dt, *J* = 16.0, 6.4 Hz, 1 H), 5.03 (dd, *J* = 6.4, 1.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, *J* = 27.5 Hz), 161.8 (t, *J* = 30.6 Hz), 147.7, 142.2, 135.5, 133.2, 131.0 (t, *J* = 1.9 Hz), 130.2 (t, *J* = 2.5 Hz), 129.3, 127.6, 125.8, 124.3, 110.2 (t, *J* = 264.4 Hz), 67.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.0 (s, 2 F). IR (film) 3076, 1774, 1701, 1597, 1518, 1344, 1310, 1159, 1126, 1105, 922, 860, 822, 744, 714, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{12}F_2NO_5$ $[M-H]^+$ 360.0684, found 360.0669. mp 65–66 °C.

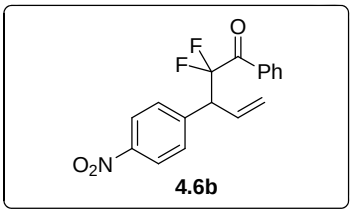


4.5b

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

General procedure E was followed using **4.4b** (108 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). The reaction temperature was raised to 70 °C. Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.5b** as a light yellow solid (41.9 mg, 44%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, *J* = 8.8 Hz,

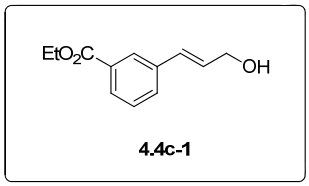
2 H), 8.14 (dd, *J* = 8.6, 1.4 Hz, 2 H), 7.66 (tt, *J* = 7.6, 1.5 Hz, 1 H), 7.55–7.49 (m, 4 H), 6.68 (d, *J* = 16.0 Hz, 1 H), 6.43 (dt, *J* = 16.0, 7.4 Hz, 1 H), 3.20 (tdd, *J* = 16.8, 7.4, 1.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.9 (t, *J* = 31.2 Hz), 147.3, 143.1, 134.8, 134.4, 131.8 (t, *J* = 3.1 Hz), 130.4 (t, *J* = 3.1 Hz), 129.0, 127.1, 124.4 (t, *J* = 5.0 Hz), 124.2, 118.7 (t, *J* = 253.1 Hz), 37.9 (t, *J* = 23.8 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.4 (t, *J* = 16.9 Hz, 2 F). IR (film) 3076, 1697, 1597, 1514, 1344, 1202, 1111, 1032, 972, 860, 716, 687, 667 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{17}H_{14}F_2NO_3$ $[M+H]^+$ 318.0942, found 318.0935. mp 81–82 °C.



4.6b

2,2-difluoro-3-(4-nitrophenyl)-1-phenylpent-4-en-1-one (4.6b)

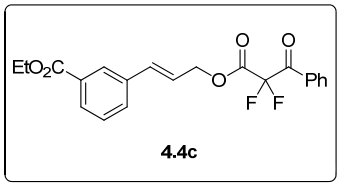
General procedure F was followed using **4.4b** (108 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.6b** as a yellow solid (74.4 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, *J* = 8.8 Hz, 2 H), 8.01 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.67–7.63 (m, 1 H), 7.56–7.48 (m, 4 H), 6.18 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1 H), 5.39 (d, *J* = 10.4 Hz, 1 H), 5.26 (d, *J* = 16.8 Hz, 1 H), 4.50 (td, *J* = 16.0, 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.9 (t, *J* = 30.0 Hz), 147.7, 143.1, 134.7, 132.4 (t, *J* = 2.5 Hz), 131.4 (t, *J* = 4.4 Hz), 130.8, 130.2 (t, *J* = 3.8 Hz), 129.0, 123.9, 122.0, 118.3 (t, *J* = 258.1 Hz), 53.5 (t, *J* = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.8 (dd, A of ABX, J_{AB} = 285.8 Hz, J_{AX} = 15.0 Hz, 1 F), –101.7 (dd, B of ABX, J_{AB} = 285.8 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 3084, 1701, 1599, 1524, 1448, 1348, 1176, 1053, 922, 833, 717, 694, 667 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{17}H_{14}F_2NO_3$ $[M+H]^+$ 318.0942, found 318.0927. mp 64–65 °C.



4.4c-1

(*E*)-ethyl 3-(3-hydroxyprop-1-en-1-yl)benzoate (4.4c-1)

Compound **4.4c-1** was prepared according to a previous report.[10] An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (0.14 g, 0.60 mmol), PPh_3 (0.32 g, 1.2 mmol), and AgOAc (2.0 g, 12 mmol). The vessel was evacuated and backfilled with $N_{2(g)}$ three times. Dry DMF (18 mL) was added *via* a syringe, followed by addition of allyl alcohol (1.6 mL, 24 mmol) at rt. The reaction tube was sealed under $N_{2(g)}$ flow, placed in a pre-heated oil bath at 70 °C, and stirred for 16 h. The tube was removed from the oil bath, and allowed to cool to rt. The reaction mixture was filtered through a pad of celite. The filtrate was added with H_2O (15 mL), and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (20% to 40%) for elution to afford the compound **4.4c-1** as a as a tan oil (0.93 g, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (t, *J* = 2.0 Hz, 1 H), 7.93 (dd, *J* = 6.6, 1.4 Hz, 1 H), 7.57 (dd, *J* = 6.8, 1.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 6.67 (dt, *J* = 15.6, 1.6 Hz, 1 H), 6.46 (dt, *J* = 15.6, 5.4 Hz, 1 H), 4.42–4.36 (m, 4 H), 1.56 (br, 1 H), 1.41 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 137.2, 131.1, 130.9, 130.2, 130.0, 128.9, 128.8, 127.7, 63.7, 61.3, 14.6. IR (film) 3458, 2982, 2868, 1716, 1443, 1367, 1288, 1261, 1198, 1105, 1022, 966, 746, 685 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1021, found 207.1020.

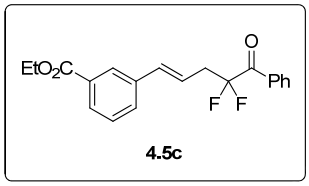


4.4c

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

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), **4.4c-1** (0.83 g, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), DMF

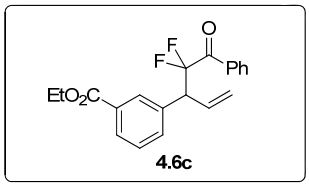
(1.2 mL), and CH_2Cl_2 (24 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **4.4c** as a light yellow oil (1.1 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, *J* = 8.4, 1.6 Hz, 2 H), 8.03 (t, *J* = 1.6 Hz, 1 H), 7.97 (dt, *J* = 7.6, 1.6 Hz, 1 H), 7.69–7.65 (m, 1 H), 7.55–7.50 (m, 3 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 16.0 Hz, 1 H), 6.31 (dt, *J* = 16.0, 6.4 Hz, 1 H), 5.00 (dd, *J* = 6.4, 1.2 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5 (t, *J* = 27.5 Hz), 166.5, 161.9 (t, *J* = 30.0 Hz), 136.1, 135.4, 135.2, 131.2, 131.1, 130.2 (t, *J* = 2.5 Hz), 129.6, 129.2, 128.9, 128.0, 122.2, 110.0 (t, *J* = 263.8 Hz), 67.8, 61.4, 14.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F). IR (film) 2982, 1774, 1718, 1599, 1450, 1306, 1275, 1202, 1159, 1105, 922, 748, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{18}F_2O_5Na$ $[M+Na]^+$ 411.1020, found 411.1007.



4.5c

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

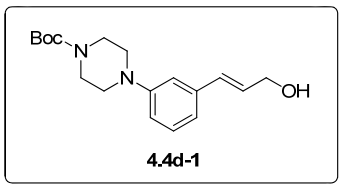
General procedure E was followed using **4.4c** (116 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.5c** as a colorless oil (86.0 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dt, *J* = 8.4, 1.2 Hz, 2 H), 8.05 (t, *J* = 1.8 Hz, 1 H), 7.93 (dt, *J* = 7.6, 1.6 Hz, 1 H), 7.64 (tt, *J* = 7.4, 1.6 Hz, 1 H), 7.56–7.49 (m, 3 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 16.0 Hz, 1 H), 6.30 (dt, *J* = 16.0, 7.2 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 3.16 (tdd, *J* = 17.2, 7.2, 1.5 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (t, *J* = 31.2 Hz), 166.6, 137.1, 135.4, 134.6, 132.0 (t, *J* = 2.5 Hz), 131.0, 130.7, 130.4 (t, *J* = 3.1 Hz), 128.9, 128.8, 127.6, 120.4 (t, *J* = 5.6 Hz), 118.8 (t, *J* = 253.1 Hz), 61.2, 37.9 (t, *J* = 23.1 Hz), 14.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.8 (t, *J* = 16.9 Hz, 2 F). IR (film) 2982, 1718, 1599, 1448, 1286, 1200, 1173, 1107, 1024, 968, 752, 716, 687, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{18}F_2O_3Na$ $[M+Na]^+$ 367.1122, found 367.1104.



4.6c

ethyl 3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-3-yl)benzoate (4.6c)

General procedure F was followed using **4.4c** (116 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.6c** as a colorless oil (86.0 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03–7.97 (m, 4 H), 7.62 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 6.22 (ddd, *J* = 16.8, 10.4, 8.4 Hz, 1 H), 5.33 (dd, *J* = 10.4, 1.2 Hz, 1 H), 5.23 (dt, *J* = 17.2, 1.2 Hz, 1 H), 4.47–4.36 (m, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.6 (t, *J* = 30.0 Hz), 166.4, 135.9, 134.4, 134.2, 132.8 (t, *J* = 2.5 Hz), 132.2 (dd, *J* = 5.0, 3.8 Hz), 131.0, 130.1 (t, *J* = 3.1 Hz), 129.2, 128.9, 128.8, 121.2, 118.6 (t, *J* = 257.5 Hz), 61.3, 53.8 (t, *J*= 21.9 Hz), 14.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.8 (dd, A of ABX, J_{AB} = 278.2 Hz, J_{AX} = 18.8 Hz, 1 F), –102.3 (dd, B of ABX, J_{AB} = 278.2 Hz, J_{BX} = 11.3 Hz, 1 F). IR (film) 2984, 1718, 1597, 1448, 1367, 1282, 1180, 1107, 1051, 933, 750, 719, 694 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{18}F_2O_3Na$ $[M+Na]^+$ 367.1122, found 367.1104.

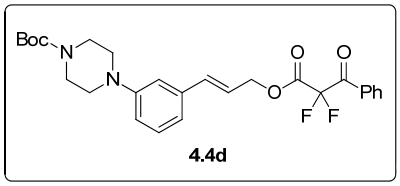


4.4d-1

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

An oven-dried Schlenk tube was charged with Pd_2dba_3 (46 mg, 0.050 mmol), DavePhos (47 mg, 0.12 mmol), and 1-*N*-Boc-piperazine (1.1 g, 6.0 mmol). The vessel was evacuated and backfilled with $N_{2(g)}$ three times. Dry THF (5.0 mL) was added *via* a syringe, followed by drop wise addition of LHMDS (1.1 M in THF/ethylbenzene, 0.010 L, 11 mmol). The reaction mixture was stirred at rt for 5 min, and then a solution of (*E*)-3-(3-bromophenyl)prop-2-en-1-ol (1.1 g, 5.0 mmol) dissolved in dry THF (2.0 mL) was

added. The reaction tube was sealed under $N_{2(g)}$ flow, placed in a pre-heated oil bath at 65 °C, and stirred for 7 h. The tube was removed from the oil bath, and allowed to cool to rt. The reaction mixture was diluted with EtOAc (20 mL), and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 40%) for elution to afford the compound **4.4d-1** as a as a tan solid (1.0 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (t, *J* = 8.2 Hz, 1 H), 6.96–6.94 (m, 2 H), 6.85–6.83 (m, 1 H), 6.59 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.36 (dt, *J* = 16.0, 5.6 Hz, 1 H), 4.33 (d, *J* = 4.8 Hz, 2 H), 3.59 (t, *J* = 5.2 Hz, 4 H), 3.15 (t, *J* = 5.2 Hz, 4 H), 1.50 (s, 9 H). HRMS (ESI, *m/z*): calcd for $C_{18}H_{26}N_2O_3Na$ $[M+Na]^+$ 341.1841, found 341.1827. Spectroscopic data matched that from the previous report.[9]

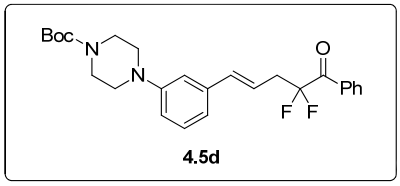


4.4d

(*E*)-*tert*-butyl-4-(3-(3-((2,2-difluoro-3-oxo-3-phenylpropanoyl)oxy)prop-1-en-1-yl)phenyl)piperazine-1-carboxylate (4.4d)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.5 g, 5.8 mmol), oxalyl chloride (0.38 mL, 4.5 mmol), **4.4d-1** (1.4 g, 4.5 mmol), Et_3N (1.2 mL, 8.9 mmol), DMF (1.2 mL), and CH_2Cl_2 (45 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **4.4d** as a tan solid (1.5 g, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 7.6 Hz, 2 H), 7.69–7.65 (m, 1 H), 7.52 (t, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 6.91–6.86 (m, 3 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.21 (dt, *J* = 16.0, 6.8 Hz, 1 H), 4.97 (dd, *J* = 6.8, 1.2 Hz, 2 H), 3.59 (t, *J* = 5.2 Hz, 4 H), 3.14 (t, *J* = 5.2 Hz, 4 H), 1.50 (s, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 154.9, 151.8, 136.8, 135.4, 131.2, 130.2 (t, J = 2.5 Hz), 129.6, 129.2, 120.9, 119.1, 117.1, 115.2, 110.1 (t, J = 263.8 Hz), 80.2, 68.2, 49.6, 43.7, 28.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3

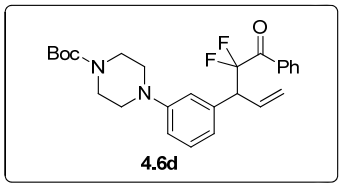
(s, 2 F). IR (film) 2976, 2822, 1774, 1693, 1597, 1450, 1421, 1242, 1163, 1124, 999, 922, 773, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{27}H_{30}F_2N_2O_5Na$ $[M+Na]^+$ 523.2020, found 523.1995. mp 81–82 °C.



4.5d

(*E*)-*tert*-butyl-4-(3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-1-yl)phenyl)piperazine-1-carboxylate (4.5d)

General procedure E was followed using **4.4d** (0.150 g, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), *t*-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.5d** as a red oil (118 mg, 86%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.67–7.63 (m, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 6.93–6.91 (m, 2 H), 6.85–6.82 (m, 1 H), 6.56 (d, *J* = 15.6 Hz, 1 H), 6.18 (dt, *J* = 15.6, 7.2 Hz, 1 H), 3.59 (t, *J* = 5.2 Hz, 4 H), 3.18–3.06 (m, 6 H), 1.50 (s, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, *J* = 31.2 Hz), 154.9, 151.8, 137.8, 136.7, 134.6, 132.2 (t, *J* = 2.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.6, 128.9, 119.0 (t, *J* = 5.6 Hz), 118.9 (t, *J* = 252.5 Hz), 118.8, 116.5, 114.9, 80.1, 49.7, 43.8, 38.0 (t, *J* = 23.8 Hz), 28.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.8 (t, *J* = 16.9 Hz, 2 F). IR (film) 2976, 1697, 1597, 1421, 1366, 1242, 1171, 1122, 997, 968, 777, 716, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{26}H_{30}F_2N_2O_3Na$ $[M+Na]^+$ 479.2122, found 479.2108.

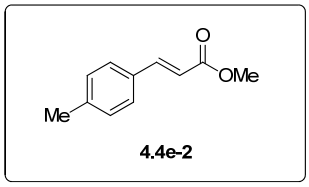


4.6d

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

General procedure F was followed using **4.4d** (0.150 g, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.6d** as a yellow oil (107 mg, 78%). ^1H NMR

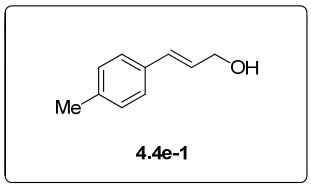
($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 8.0 Hz, 2 H), 7.63–7.58 (m, 1 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.23–7.19 (m, 1 H), 6.86–6.81 (m, 3 H), 6.20 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1 H), 5.30 (d, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 17.2 Hz, 1 H), 4.26 (td, *J* = 16.4, 8.4 Hz, 1 H), 3.56 (t, *J* = 5.2 Hz, 4 H), 3.08 (t, *J* = 5.2 Hz, 4 H), 1.49 (s, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.1 (t, *J* = 29.4 Hz), 154.9, 151.6, 136.2, 134.2, 133.2, 132.5 (t, *J* = 4.4 Hz), 130.0 (t, *J* = 3.1 Hz), 129.6, 128.8, 121.6, 120.7, 118.8 (t, *J* = 256.9 Hz), 118.2, 116.2, 80.1, 54.5 (t, *J* = 21.9 Hz), 49.5, 43.6, 28.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.8 (dd, A of ABX, J_{AB} = 270.7 Hz, J_{AX} = 15.0 Hz, 1 F), –102.6 (dd, B of ABX, J_{AB} = 270.7 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 2976, 2860, 1697, 1601, 1450, 1421, 1366, 1236, 1171, 1124, 1051, 997, 932, 868, 775, 698 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{26}H_{30}F_2N_2O_3Na$ $[M+Na]^+$ 479.2122, found 479.2130.



4.4e-2

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

General procedure B was followed using 4-methylcinnamic acid (1.95 g, 12.0 mmol), thionyl chloride (1.7 mL, 24 mmol), and MeOH (25 mL). Workup afforded the title compound **4.4e-2** as a colorless solid (1.99 g, 94%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 16.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 3.81 (s, 3 H), 2.38 (s, 3 H). Spectroscopic data of ^1H NMR matched that from the previous report.[11]

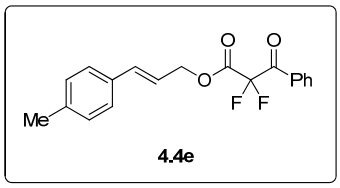


4.4e-1

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

General procedure C was followed using **4.4e-2** (1.41 g, 8.00 mmol), DIBAL (1.0 M in hexane, 0.020 L, 0.020 mmol), and CH_2Cl_2 (0.020 L). Workup afforded the title compound **4.4e-1** as a colorless solid (1.15 g, 97%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.60 (dt, *J* =

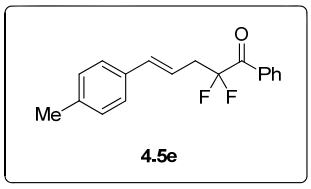
16.0, 1.4 Hz, 1 H), 6.33 (dt, *J* = 16.0, 5.8 Hz, 1 H), 4.32 (td, *J* = 5.8, 1.4 Hz, 2 H), 2.36 (s, 3 H), 1.59 (t, *J* = 5.8 Hz, 1 H). Spectroscopic data of ^{1}H NMR matched that from the previous report.[12]



4.4e

(*E*)-3-(*p*-tolyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4e)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.4 g, 5.4 mmol), oxalyl chloride (0.38 mL, 4.5 mmol), **4.4e-1** (0.67 g, 4.5 mmol), Et_3N (1.2 mL, 9.0 mmol), DMF (1.2 mL), and CH_2Cl_2 (25 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.4e** as a colorless oil (1.1 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, *J* = 8.8, 1.2 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.54–7.49 (m, 2 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.18 (dt, *J* = 15.6, 6.8 Hz, 1 H), 4.96 (dd, *J* = 6.4, 1.2, 2 H), 2.36 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 138.7, 136.6, 135.3, 133.0, 131.2 (t, *J* = 1.9 Hz), 130.2 (t, *J* = 2.5 Hz), 129.5, 129.2, 126.9, 119.8, 110.0 (t, *J* = 263.1 Hz), 68.4, 21.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (s, 2 F). IR (film) 3028, 2921, 1774, 1713, 1699, 1599, 1514, 1450, 1310, 1159, 1124, 1101, 970, 922, 795, 712, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{16}F_2O_3Na$ $[M+Na]^+$ 353.0965, found 353.0962.

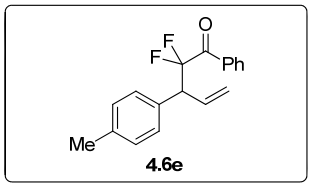


4.5e

(*E*)-2,2-difluoro-1-phenyl-5-(*p*-tolyl)pent-4-en-1-one (4.5e)

General procedure E was followed using **4.4e** (99.1 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.5e** as an off-white solid (75.0 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.65 (tt, *J* = 7.4, 1.5 Hz, 1 H),

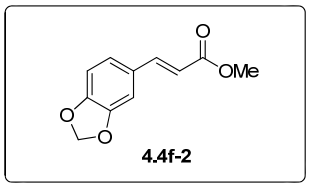
7.54–7.50 (m, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.57 (d, J = 16.0 Hz, 1 H), 6.17 (dt, J = 16.0, 7.4 Hz, 1 H), 3.14 (tdd, J = 17.0, 7.4, 1.5 Hz, 2 H), 2.36 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, J = 31.2 Hz), 137.8, 136.3, 134.5, 134.1, 130.4 (t, J = 3.1 Hz), 129.4, 128.9, 126.5, 118.9 (t, J = 252.5 Hz), 117.8 (t, J = 5.0 Hz), 38.1 (t, J = 23.8 Hz), 21.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –99.0 (t, J = 18.8 Hz, 2 F). IR (film) 3038, 2922, 1703, 1599, 1514, 1448, 1273, 1173, 1120, 968, 804, 716, 687, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{17}F_2O$ $[M+H]^+$ 287.1247, found 287.1243. m.p. 50–52 °C.



4.6e

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

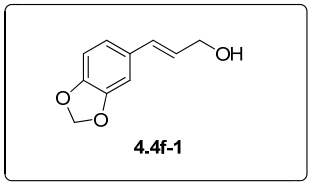
General procedure F was followed using **4.4e** (99.1 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.6e** as a light yellow oil (77.0 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (dt, J = 7.6, 1.2 Hz, 2 H), 7.61 (tt, J = 7.4, 1.4 Hz, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.22 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.30 (dd, J = 10.4, 1.2 Hz, 1 H), 5.22 (dt, J = 17.2, 1.2 Hz, 1 H), 4.29 (td, J = 16.6, 8.4 Hz, 1 H), 2.33 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.1 (t, J = 29.4 Hz), 137.8, 134.2, 133.1, 132.8 (t, J = 3.8 Hz), 132.2 (t, J = 2.5 Hz), 130.1 (t, J = 3.8 Hz), 129.6, 129.5, 128.8, 120.5, 118.8 (t, J = 256.9 Hz), 53.8 (t, J = 21.2 Hz), 21.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.6 (dd, A of ABX, J_{AB} = 274.5 Hz, J_{AX} = 16.9 Hz, 1 F), –103.2 (dd, B of ABX, J_{AB} = 274.5 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 3026, 2922, 1705, 1597, 1516, 1448, 1267, 1174, 1049, 924, 795, 714, 688, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2ONa$ $[M+Na]^+$ 309.1067, found 309.1064.



4.4f-2

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

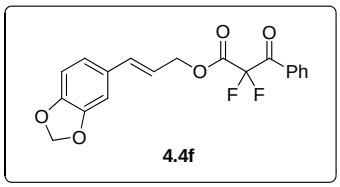
General procedure B was followed using 3,4-(methylenedioxyl)cinnamic acid (2.00 g, 10.4 mmol), thionyl chloride (1.5 mL, 21 mmol), and MeOH (15 mL). Workup afforded the title compound **4.4f-2** as a colorless solid (2.05 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, *J* = 16.0 Hz, 1 H), 7.04 (d, *J* = 1.6 Hz, 1 H), 7.01 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.28 (d, *J* = 16.0 Hz, 1 H), 6.02 (s, 2 H), 3.80 (s, 3 H). HRMS (ESI, *m/z*): calcd for $C_{11}H_{10}O_4Na$ $[M+Na]^+$ 229.0477, found 229.0494. Spectroscopic data matched that from the previous report.[13]



4.4f-1

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

General procedure C was followed using **4.4f-2** (1.50 g, 7.30 mmol), DIBAL (1.0 M in hexane, 15 mL, 15 mmol), and CH_2Cl_2 (15 mL). Workup afforded the title compound **4.4f-1** as a colorless solid (1.27 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (d, *J* = 1.6 Hz, 1 H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 6.53 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.21 (dt, *J* = 16.0, 6.0 Hz, 1 H), 5.97 (s, 2 H), 4.30 (d, *J* = 6.0 Hz, 2 H), 1.45 (br, 1 H). HRMS (ESI, *m/z*): calcd for $C_{10}H_{11}O_3$ $[M+H]^+$ 179.0708, found 179.0716. Spectroscopic data matched that from the previous report.13

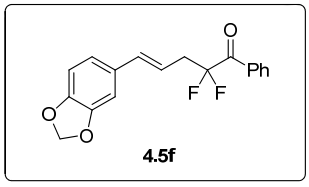


4.4f

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

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.6 g, 6.0 mmol), oxalyl chloride (0.42 mL, 5.0 mmol), **4.4f-1** (0.89 g, 5.0 mmol), Et_3N (1.4 mL, 0.010 mol), DMF (1.2 mL), and CH_2Cl_2 (25 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound **4.4f** as a colorless oil (1.3 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ

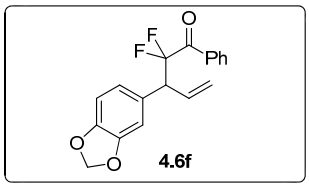
8.08 (d, *J* = 8.0 Hz, 2 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 6.89 (d, *J* = 1.6 Hz, 1 H), 6.82–6.75 (m, 2 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.05 (dt, *J* = 16.0, 6.8 Hz, 1 H), 5.98 (s, 2 H), 4.94 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 148.3, 148.2, 136.4, 135.3, 131.2, 130.2, 130.1 (t, *J* = 2.5 Hz), 129.2, 122.1, 118.9, 110.0 (t, *J* = 263.8 Hz), 108.5, 106.1, 101.4, 68.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (s, 2 F). IR (film) 2895, 1774, 1711, 1699, 1504, 1491, 1448, 1308, 1252, 1159, 1040, 922, 712, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{15}F_2O_5$ $[M+H]^+$ 361.0888, found 361.0897.



4.5f

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

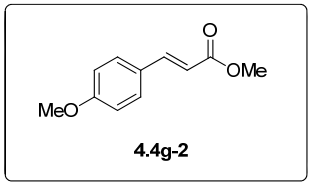
General procedure E was followed using **4.4f** (108 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.5f** as an off-white solid (66.0 mg, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dt, *J* = 8.0, 1.2 Hz, 2 H), 7.67–7.62 (m, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 1.6 Hz, 1 H), 6.81–6.74 (m, 2 H), 6.49 (d, *J* = 16.0 Hz, 1 H), 6.03 (dt, *J* = 16.0, 7.2 Hz, 1 H), 5.95 (s, 2 H), 3.10 (tdd, *J* = 17.2, 7.2, 1.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, *J* = 30.6 Hz), 148.2, 147.5, 135.9, 134.5, 132.2 (t, *J* = 1.9 Hz), 131.4, 130.4 (t, *J* = 3.1 Hz), 128.9, 121.3, 118.9 (t, *J* = 252.5 Hz), 117.1 (t, *J* = 5.0 Hz), 108.4, 105.9, 101.3, 38.0 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –99.0 (t, *J* = 16.9 Hz, 2 F). IR (film) 3072, 2899, 1701, 1597, 1504, 1491, 1448, 1252, 1173, 1040, 966, 933, 804, 714, 687, 669 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{14}F_2O_3Na$ $[M+Na]^+$ 339.0809, found 339.0800. mp 77–78 °C.



4.6f

3-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-1-phenylpent-4-en-1-one (4.6f)

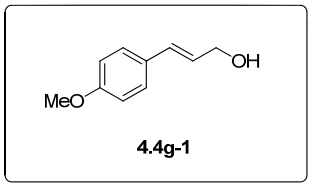
General procedure F was followed using **4.4f** (108.1 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.6f** as a colorless oil (77.6 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.62 (tt, *J* = 7.6, 1.4 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 2 H), 6.84 (s, 1 H), 6.74 (s, 2 H), 6.16 (ddd, *J* = 16.8, 10.4, 8.2 Hz, 1 H), 5.95 (s, 2 H), 5.30 (d, *J* = 10.0 Hz, 1 H), 5.22 (dt, *J* = 16.8, 1.2 Hz, 1 H), 4.24 (td, *J* = 16.2, 8.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0 (t, *J* = 29.4 Hz), 148.0, 147.4, 134.3, 133.1, 132.6 (t, *J* = 3.8 Hz), 130.1 (t, *J* = 3.1 Hz), 128.8, 123.4, 120.6, 118.7 (t, *J* = 257.5 Hz), 110.0, 108.5, 101.3, 53.7 (t, *J* = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.1 (dd, A of ABX, J_{AB} = 274.5 Hz, J_{AX} = 15.0 Hz, 1 F), –103.0 (dd, B of ABX, J_{AB} = 274.5 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 3076, 2893, 1705, 1597, 1504, 1489, 1446, 1250, 1182, 1040, 932, 800, 719, 688, 669 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{14}F_2O_3Na$ $[M+Na]^+$ 339.0809, found 339.0824.



4.4g-2

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

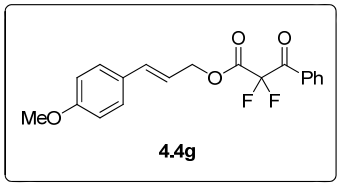
General procedure B was followed using 4-methoxycinnamic acid (5.0 g, 28 mmol), thionyl chloride (4.1 mL, 56 mmol), and MeOH (45 mL). Workup afforded the title compound **4.4g-2** as a colorless solid (5.3 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 16.0 Hz, 1 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.32 (d, *J* = 16.0 Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H). Spectroscopic data of ^{1}H NMR matched that from the previous report.[11]



4.4g-1

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

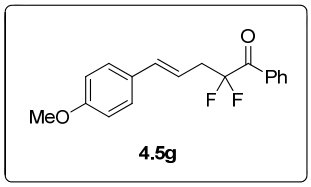
General procedure C was followed using **4.4g-2** (2.20 g, 11.4 mmol), DIBAL (1.0 M in hexane, 28.6 mL, 28.6 mmol), and CH_2Cl_2 (30.0 mL). Workup afforded the title compound **4.4g-1** as a colorless solid (1.84 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.57 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.25 (dt, *J* = 16.0, 6.0 Hz, 1 H), 4.31 (d, *J* = 5.6 Hz, 2 H), 3.82 (s, 3 H), 1.42 (br, 1 H). HRMS (ESI, *m/z*): calcd for $C_{10}H_{13}O_2$ $[M+H]^+$ 165.0916, found 165.0911. Spectroscopic data matched that from the previous report.[14]



4.4g

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

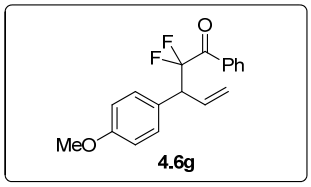
General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.6 g, 6.0 mmol), oxalyl chloride (0.42 mL, 5.0 mmol), **4.4g-1** (0.82 g, 5.0 mmol), Et_3N (1.4 mL, 0.010 mol), DMF (1.2 mL), and CH_2Cl_2 (25 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound **4.4g** as a colorless solid (0.94 g, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (dt, *J* = 7.6, 1.2 Hz, 2 H), 7.66 (tt, *J* = 7.6, 1.4 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.64 (d, *J* = 16.0 Hz, 1 H), 6.09 (dt, *J* = 16.0, 6.8 Hz, 1 H), 4.95 (dd, *J* = 6.8, 1.2 Hz, 2 H), 3.82 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 160.1, 136.4, 135.3, 131.2 (t, *J* = 1.2 Hz), 130.2 (t, *J*= 2.5 Hz), 129.2, 128.5, 128.3, 118.5, 114.2, 110.0 (t, *J* = 263.8 Hz), 68.6, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.4 (s, 2 F). IR (film) 2959, 2837, 1774, 1711, 1701, 1606, 1512, 1450, 1306, 1252, 1159, 922, 845, 711, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{16}F_2O_4Na$ $[M+Na]^+$ 369.0914, found 369.0898. mp 36–38 °C.



4.5g

(*E*)-2,2-difluoro-5-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (4.5g)

General procedure E was followed using **4.4g** (104 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.5g** as an off-white solid (52.0 mg, 57%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.66–7.62 (m, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.53 (d, *J* = 16.0 Hz, 1 H), 6.06 (dt, *J* = 16.0, 7.2 Hz, 1 H), 3.12 (tdd, *J* = 17.2, 7.2, 1.4 Hz, 2 H), 3.81 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.5 (t, *J* = 30.6 Hz), 159.5, 135.8, 134.5, 132.2 (t, *J* = 2.5 Hz), 130.4 (t, *J* = 3.1 Hz), 129.7, 128.9, 127.8, 118.9 (t, *J* = 252.5 Hz), 116.6 (t, *J* = 5.0 Hz), 114.1, 55.5, 38.1 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –99.0 (t, *J* = 16.9 Hz, 2 F). IR (film) 2959, 1701, 1606, 1512, 1448, 1250, 1174, 1036, 968, 837, 806, 714, 687, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2O_2Na$ $[M+Na]^+$ 325.1016, found 325.1005. mp 55–57 °C.

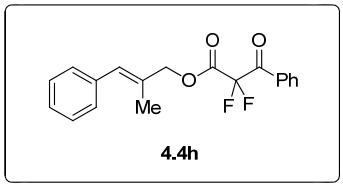


4.6g

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

General procedure F was followed using **4.4g** (104 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.6g** as a colorless oil (65.1 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.61 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.20 (ddd, *J* = 17.2, 10.2, 8.0 Hz, 1 H), 5.30 (d, *J* = 10.4 Hz, 1 H), 5.20 (dd, *J* = 17.2, 1.6 Hz, 1 H), 4.27 (td, *J* = 16.4, 8.0 Hz, 1 H), 3.79 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.2 (t, *J* = 30.0 Hz), 159.4, 134.2, 133.1, 132.8 (t, *J* = 4.4 Hz), 130.9, 130.1 (t, *J* = 3.8 Hz), 128.8, 127.2, 120.4, 118.8 (t, *J* =256.9 Hz), 114.2, 55.4, 53.4 (t, *J* = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.1 (dd, A of ABX, J_{AB} = 274.5 Hz, J_{AX} = 16.0 Hz, 1 F), –103.0 (dd, B of ABX, J_{AB} =

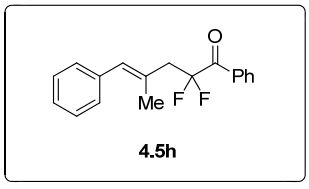
274.5 Hz, J_{BX} = 16.0 Hz, 1 F). IR (film) 2957, 1703, 1612, 1599, 1514, 1448, 1252, 1180, 1036, 922, 804, 714, 688, 667 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2O_2Na$ [M+Na]$^+$ 325.1016, found 325.1001.



4.4h

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

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), *trans*-2-methyl-3-phenyl-2-propen-1-ol (0.59 g, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), DMF (1.2 mL), and CH_2Cl_2 (24 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.4h** as a colorless oil (0.94 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, *J* = 8.4 Hz, 2 H), 7.70–7.66 (m, 1 H), 7.53 (t, *J* = 8.0 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.28–7.23 (m, 3 H), 6.56 (s, 1 H), 4.89 (s, 2 H), 1.83 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6 (t, *J* = 26.9 Hz), 161.9 (t, *J* = 30.6 Hz), 136.6, 135.4, 131.2 (t, *J* = 1.9 Hz), 131.0, 130.6, 130.2 (t, *J* = 2.5 Hz), 129.2, 129.1, 128.4, 127.3, 110.0 (t, *J* = 263.1 Hz), 73.4, 15.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.3 (s, 2 F). IR (film) 3062, 2949, 1776, 1713, 1699, 1599, 1450, 1306, 1157, 1101, 922, 746, 698, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{16}F_2O_3Na$ [M+Na]$^+$ 353.0965, found 353.0952.

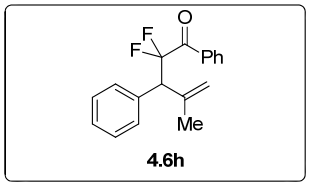


4.5h

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

General procedure E was followed using **4.4h** (99.1 mg, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), *t*-BuBrettPhos (15 mg, 0.030 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.5h** as a colorless oil (67 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, *J* = 7.6 Hz, 2 H), 7.66 (tt, *J* = 7.6, 1.5 Hz, 1 H), 7.52 (t, *J* =

7.6 Hz, 2 H), 7.37–7.33 (m, 2 H), 7.26–7.22 (m, 3 H), 6.41 (s, 1 H), 3.10 (t, J = 17.8 Hz, 2 H), 2.01 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.9 (t, J = 30.0 Hz), 137.6, 134.4, 132.5 (t, J = 1.9 Hz), 132.2, 130.3 (t, J = 3.1 Hz), 129.2 (t, J = 3.1 Hz), 129.1, 128.9, 128.3, 126.8, 119.4 (t, J = 253.1 Hz), 44.8 (t, J = 22.5 Hz), 19.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.3 (t, J = 18.8 Hz, 2 F). IR (film) 3059, 2922, 1703, 1599, 1448, 1277, 1176, 1113, 1061, 1028, 918, 744, 716, 698, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2ONa$ $[M+Na]^+$ 309.1067, found 309.1059.

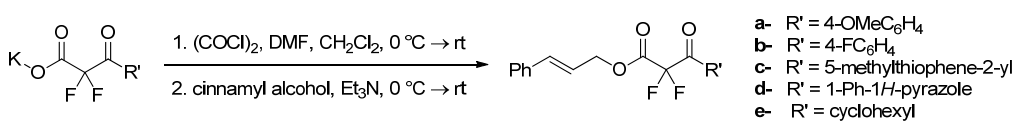


4.6h

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

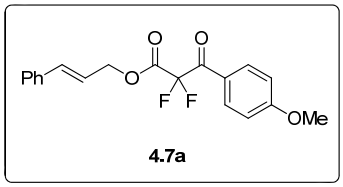
General procedure F was followed using **4.4h** (99.1 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.6h** as a colorless oil (71 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.41–7.32 (m, 5 H), 5.08 (s, 1 H), 5.05 (s, 1 H), 4.31 (dd, J = 21.6, 14.4 Hz, 1 H), 1.74 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.3 (t, J = 30.0 Hz), 140.9 (d, J = 5.0 Hz), 134.5 (d, J = 2.5 Hz), 134.1, 133.2, 130.2, 130.0 (t, J = 3.1 Hz), 128.8, 128.6, 128.0, 119.1 (dd, J = 260.0, 253.8 Hz), 115.5 (d, J = 3.8 Hz), 55.7 (t, J = 20.6 Hz), 23.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.2 (dd, A of AMX, J_{AM} = 282.0 Hz, J_{AX} = 22.6 Hz, 1 F), –97.1 (dd, M of AMX, J_{AM} = 282.0 Hz, J_{MX} = 13.2 Hz, 1 F). IR (film) 3063, 2974, 1701, 1597, 1493, 1450, 1282, 1184, 1120, 1051, 922, 741, 717, 698, 665, 604 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2ONa$ $[M+Na]^+$ 309.1067, found 309.1069.

Experimental Procedures and Characterization of Compounds in Scheme 4.12



a- R' = 4-$OMeC_6H_4$
b- R' = 4-FC_6H_4
c- R' = 5-methylthiophene-2-yl
d- R' = 1-Ph-1*H*-pyrazole
e- R' = cyclohexyl

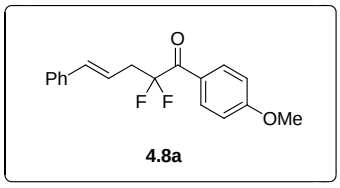
4.7a–4.7e



4.7a

cinnamyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (4.7a)

General procedure D was followed using potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate[3] (1.5 g, 5.6 mmol), oxalyl chloride (0.52 mL, 6.2 mmol), cinnamyl alcohol (1.1 g, 8.4 mmol), Et_3N (0.93 mL, 6.7 mmol), DMF (1.0 mL), and CH_2Cl_2 (0.020 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **4.7a** as a colorless oil (1.6 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.8 Hz, 2 H), 7.37–7.28 (m, 5 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.68 (dt, *J* = 16.0, 1.2 Hz, 1 H), 6.23 (dt, *J* = 16.0, 6.4 Hz, 1 H), 4.97 (dd, *J* = 6.4, 1.2 Hz, 2 H), 3.87 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 183.8 (t, *J* = 26.9 Hz), 165.3, 162.1 (t, *J* = 30.0 Hz), 136.3, 135.8, 132.8 (t, *J* = 2.5 Hz), 128.8, 128.6, 127.0, 124.0 (t, *J* = 1.9 Hz), 121.0, 114.5, 110.3 (t, *J* = 263.1 Hz), 68.0, 55.8. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.1 (s, 2 F). IR (film) 3028, 2960, 1774, 1701, 1690, 1601, 1574, 1512, 1427, 1312, 1269, 1157, 1099, 1026, 968, 924, 845, 746, 692, 579 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{16}F_2O_4Na$ $[M+Na]^+$ 369.0914, found 369.0896.

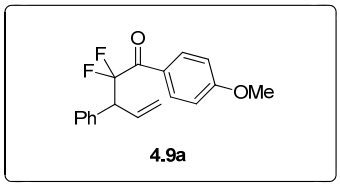


4.8a

(*E*)-2,2-difluoro-1-(4-methoxyphenyl)-5-phenylpent-4-en-1-one (4.8a)

General procedure E was followed using **4.7a** (104 mg, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), *t*-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.8a** as an off-white solid (72.0 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dt, *J* = 8.8, 1.2 Hz, 2 H), 7.39–7.37 (m, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.27–7.23 (m, 1 H), 6.98 (d, *J* = 9.2 Hz, 2 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 6.22 (dt, *J* = 16.0, 7.2 Hz, 1 H), 3.90 (s, 3 H), 3.12 (tdd, *J* = 17.2, 7.2, 1.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.8 (t,

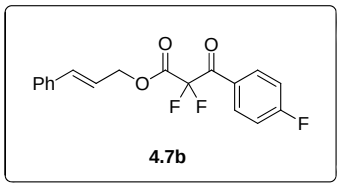
J = 30.6 Hz), 164.7, 136.9, 136.2, 133.0 (t, J = 3.1 Hz), 128.8, 127.9, 126.6, 125.0 (t, J = 2.5 Hz), 119.3 (t, J = 5.0 Hz), 119.1 (t, J = 252.5 Hz), 114.2, 55.8, 38.2 (t, J = 23.8 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.5 (t, J = 16.9 Hz, 2 F). IR (film) 3026, 2935, 1690, 1601, 1574, 1512, 1425, 1265, 1167, 1119, 1028, 968, 845, 770, 746, 692, 619 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2O_2Na$ $[M+Na]^+$ 325.1016, found 325.0989. mp 41–42 °C.



4.9a

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

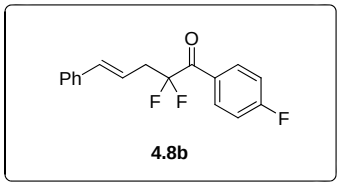
General procedure F was followed using **4.7a** (104 mg, 0.300 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), PhXPhos (9.8 mg, 0.021 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.9a** as a light yellow oil (76.0 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (dt, J = 8.8, 1.0 Hz, 2 H), 7.33–7.28 (m, 5 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.23 (ddd, J = 17.2, 10.4, 8.0 Hz, 1 H), 5.30 (d, J = 10.4 Hz, 1 H), 5.22 (dt, J = 17.2, 1.2 Hz, 1 H), 4.31 (td, J = 16.4, 8.0 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.2 (t, J = 29.4 Hz), 164.4, 135.6 (t, J = 2.5 Hz), 132.8 (t, J = 4.4 Hz), 132.7 (t, J = 3.8 Hz), 129.8, 128.8, 128.0, 125.8 (t, J = 1.9 Hz), 120.6, 119.0 (t, J = 257.5 Hz), 114.1, 55.7, 54.3 (t, J = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.9 (d, A_2, J = 15.0 Hz, 2 F). IR (film) 3030, 2935, 1691, 1601, 1574, 1510, 1456, 1423, 1315, 1265, 1178, 1117, 1028, 924, 845, 744, 700, 619 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}F_2O_2Na$ $[M+Na]^+$ 325.1016, found 325.1004.



4.7b

cinnamyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (4.7b)

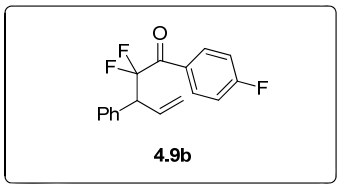
General procedure D was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate[3] (1.20 g, 4.68 mmol), oxalyl chloride (0.40 mL, 4.7 mmol), cinnamyl alcohol (0.820 g, 6.08 mmol), Et_3N (0.98 mL, 7.0 mmol), DMF (0.75 mL), and CH_2Cl_2 (16 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.7b** as a colorless oil (1.14 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dd, *J* = 8.8, 5.2 Hz, 2 H), 7.39–7.28 (m, 5 H), 7.22–7.16 (m, 2 H), 6.70 (dt, *J* = 16.0, 1.2 Hz, 1 H), 6.24 (dt, *J* = 16.0, 6.8 Hz, 1 H), 4.98 (dd, *J* = 6.8, 1.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.1 (t, *J* = 27.5 Hz), 167.1 (d, *J* = 257.5 Hz), 161.8 (t, *J* = 30.6 Hz), 136.7, 135.8, 133.2 (dt, *J* = 10.0, 2.5 Hz), 128.9, 128.8, 127.6, 127.0, 120.8, 116.6 (d, *J* = 22.5 Hz), 110.0 (t, *J* = 263.8 Hz), 68.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.2 (s, 2 F), –100.3 (m, 1 F). IR (film) 3082, 3028, 1774, 1701, 1599, 1508, 1308, 1244, 1161, 1124, 1101, 968, 924, 852, 746, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{13}F_3O_3Na$ $[M+Na]^+$ 357.0714, found 357.0701.



4.8b

(*E*)-2,2-difluoro-1-(4-fluorophenyl)-5-phenylpent-4-en-1-one (4.8b)

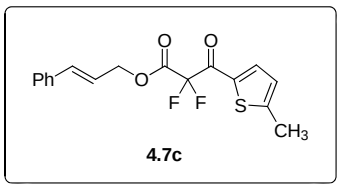
General procedure E was followed using **4.7b** (0.100 g, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.8b** as a light yellow oil (75.0 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (dd, *J* = 8.6, 5.4 Hz, 2 H), 7.39–7.37 (m, 2 H), 7.34–7.30 (m, 2 H), 7.28–7.24 (m, 1 H), 7.18 (t, *J* = 8.6 Hz, 2 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.21 (dt, *J* = 16.0, 7.4 Hz, 1 H), 3.13 (tdd, *J* = 17.2, 7.4, 1.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.8 (t, *J* = 31.2 Hz), 166.6 (d, *J* = 256.2 Hz), 136.8, 136.5, 133.3 (dt, *J* = 10.0, 3.8 Hz), 129.8, 128.8, 128.5, 128.0, 126.6, 118.9 (t, *J* = 5.0 Hz), 118.9 (t, *J* = 252.5 Hz), 37.9 (t, *J* = 23.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.2 (m, 1 F), –98.6 (t, *J* = 16.9 Hz, 2 F). IR (film) 3028, 1701, 1599, 1508, 1414, 1242, 1161, 966, 850, 766, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{13}F_3ONa$ $[M+Na]^+$ 313.0816, found 313.0830.



4.9b

2,2-difluoro-1-(4-fluorophenyl)-3-phenylpent-4-en-1-one (4.9b)

General procedure F was followed using **4.7b** (0.100 g, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.9b** as an off-white solid (74.8 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (dd, *J* = 8.6, 5.4 Hz, 2 H), 7.33–7.28 (m, 5 H), 7.12 (t, *J* = 8.6 Hz, 2 H), 6.22 (ddd, *J* = 16.8, 10.4, 8.4 Hz, 1 H), 5.32 (d, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 16.8 Hz, 1 H), 4.30 (td, *J* = 16.4, 8.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.5 (t, *J* = 29.4 Hz), 166.4 (d, *J* = 256.2 Hz), 135.2 (d, *J* = 3.8 Hz), 133.0 (dt, *J* = 8.8, 3.8 Hz), 132.5 (t, *J* = 4.4 Hz), 129.8, 129.4 (d, *J* = 2.5 Hz), 128.8, 128.1, 120.9, 118.8 (t, *J* = 256.2 Hz), 116.1 (d, *J* = 21.2 Hz), 54.1 (t, *J* = 21.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –103.4 (dd, A of ABX, J_{AB} = 276.4 Hz, J_{AX} = 16.9 Hz, 1 F), –102.6 (m, 1 F), –102.5 (dd, B of ABX, J_{AB} = 276.4 Hz, J_{BX} = 16.9 Hz, 1 F). IR (film) 3086, 1707, 1599, 1506, 1412, 1242, 1161, 1047, 926, 850, 744, 700 cm^{-1}. HRMS (APCI-hexane/PhMe, *m/z*): calcd for $C_{17}H_{14}F_3O$ $[M+H]^+$ 291.0997, found 291.0994. mp 35–36 °C.

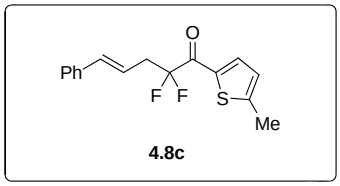


4.7c

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

General procedure D was followed using potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate[3] (1.5 g, 5.8 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), cinnamyl alcohol (1.0 g, 7.5 mmol), Et_3N (1.2 mL, 8.7 mmol), DMF (1.0 mL), and CH_2Cl_2 (21 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.7c** as a colorless oil (1.4 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87–7.86 (m, 1 H), 7.39–7.29 (m, 5 H), 6.87 (dd, *J* = 4.0, 1.2 Hz, 1 H),

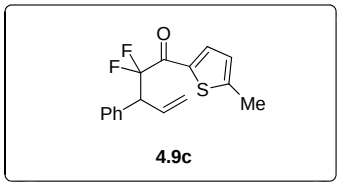
6.69 (dt, *J* = 16.0, 1.2 Hz, 1 H), 6.25 (dt, *J* = 16.0, 6.4 Hz, 1 H), 4.97 (dd, *J* = 6.4, 1.2 Hz, 2 H), 2.57 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9 (t, *J* = 28.1 Hz), 161.8 (t, *J* = 30.6 Hz), 154.6, 137.5 (t, *J* = 5.0 Hz), 136.4, 135.8, 135.2, 128.8, 128.7, 128.2, 127.0, 120.9, 109.7 (t, *J* = 263.1 Hz), 68.1, 16.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.0 (s, 2 F). IR (film) 3028, 1774, 1664, 1446, 1310, 1265, 1155, 1051, 968, 912, 812, 746, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3SNa$ $[M+Na]^+$ 359.0529, found 359.0531.



4.8c

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

General procedure E was followed using **4.7c** (101 mg, 0.300 mmol), $Pd(OAc)_2$ (2.0 mg, 0.090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.8c** as a light yellow solid (78.0 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87–7.86 (m, 1 H), 7.38–7.36 (m, 2 H), 7.34–7.30 (m, 2 H), 7.26–7.22 (m, 1 H), 6.88 (dd, *J* = 3.6, 1.2 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 6.19 (dt, *J* = 16.0, 7.4 Hz, 1 H), 3.10 (tdd, *J* = 17.0, 7.4, 1.4 Hz, 2 H), 2.58 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.3 (t, *J* = 31.2 Hz), 153.3, 136.9 (t, *J* = 5.0 Hz), 136.8, 136.4, 136.3, 128.7, 128.0, 127.9, 126.6, 118.9 (t, *J* = 5.0 Hz), 118.6 (t, *J* = 252.5 Hz), 38.2 (t, *J* = 23.8 Hz), 16.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –100.0 (t, *J* = 16.9 Hz, 2 F). IR (film) 3026, 1670, 1448, 1223, 1184, 1171, 1057, 968, 812, 758, 739, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2OSNa$ $[M+Na]^+$ 315.0631, found 315.0643. mp 49–50 °C.

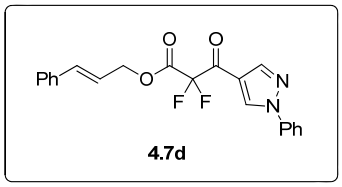


4.9c

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

General procedure F was followed using **4.7c** (101 mg, 0.300 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). The reaction time was 18 h. Workup and

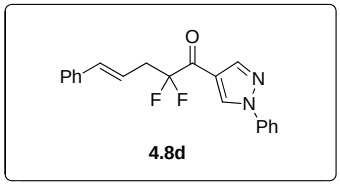
chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.9c** as a light yellow solid (76.0 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.72 (m, 1 H), 7.35–7.28 (m, 5 H), 5.81 (dd, *J* = 4.0, 1.2 Hz, 1 H), 6.22 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 5.24 (dt, *J* = 17.2, 1.2 Hz, 1 H), 4.26 (td, *J* = 16.6, 8.4 Hz, 1 H), 2.55 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.4 (t, *J* = 30.0 Hz), 153.2, 137.0, 136.6 (t, *J* = 5.6 Hz), 135.3 (t, *J* = 1.9 Hz), 132.4 (t, *J* = 3.8 Hz), 129.8, 128.7, 128.0, 127.8, 120.8, 118.7 (t, *J* = 257.5 Hz), 54.3 (t, *J* = 21.9 Hz), 16.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –104.8 (d, A_2, *J* = 15.0 Hz, 2 F). IR (film) 3030, 1662, 1448, 1275, 1171, 1061, 1040, 932, 812, 748, 719, 700 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2OSK$ $[M+K]^+$ 331.0371, found 331.0382. mp 55–56 °C.



4.7d

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

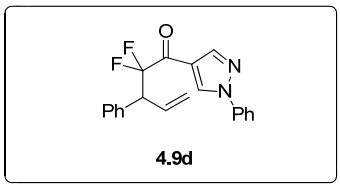
General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1*H*-pyrazol-4-yl)propanoate[3] (0.76 g, 2.5 mmol), oxalyl chloride (0.19 mL, 2.3 mmol), cinnamyl alcohol (0.28 g, 2.1 mmol), Et_3N (0.58 mL, 4.2 mmol), DMF (48 μL), and CH_2Cl_2 (12 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound **4.7d** as a colorless solid (0.68 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1 H), 8.31 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.43–7.37 (m, 3 H), 7.35–7.28 (m, 3 H), 6.72 (d, *J* = 16.0 Hz, 1 H), 6.27 (dt, *J* = 16.0, 6.4 Hz, 1 H), 4.98 (d, *J* = 6.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.9 (t, *J* = 28.8 Hz), 161.7 (t, *J* = 30.6 Hz), 143.0 (t, *J* = 2.5 Hz), 139.0, 136.6, 135.7, 131.7 (t, *J* = 3.8 Hz), 129.9, 128.9, 128.8, 128.6, 127.0, 120.8, 120.2, 118.8, 109.6 (t, *J* = 262.5 Hz), 68.3. ^{19}H NMR ($CDCl_3$, 376 MHz) δ –110.6 (s, 2F). IR (film) 3138, 3059, 1774, 1688, 1541, 1504, 1308, 1242, 1171, 1126, 1036, 968, 951, 883, 758, 690 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{16}F_2N_2O_3Na$ $[M+Na]^+$ 405.1027, found 405.1025. mp 64–65 °C.



4.8d

(*E*)-2,2-difluoro-5-phenyl-1-(1-phenyl-1*H*-pyrazol-4-yl)pent-4-en-1-one (4.8d)

General procedure E was followed using **4.7d** (76.5 mg, 0.200 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), *t*-BuBrettPhos (9.7 mg, 0.020 mmol), and 1,4-dioxane (0.40 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.8d** as a colorless solid (43 mg, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1 H), 8.29 (s, 1 H), 7.72–7.70 (m, 2 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.43–7.22 (m, 6 H), 6.61 (d, *J* = 16.0 Hz, 1 H), 6.19 (dt, *J* = 16.0, 7.4 Hz, 1 H), 3.10 (tdd, *J* = 17.0, 7.4, 1.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.3 (t, *J* = 31.9 Hz), 143.2 (t, *J* = 2.5 Hz), 139.2, 136.7, 136.6, 131.6 (t, *J* = 5.0 Hz), 129.9, 128.8, 128.4, 128.1, 126.6, 120.0, 119.6, 118.7 (t, *J* = 5.0 Hz), 118.5 (t, *J* = 251.2 Hz), 37.6 (t, *J* = 23.8 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.4 (t, *J* = 16.9 Hz, 2 F). IR (film) 1686, 1541, 1502, 1186, 1038, 951, 908, 876, 833, 756, 688 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{17}F_2N_2O$ $[M+H]^+$ 339.1309, found 339.1320. mp 95–97 °C.

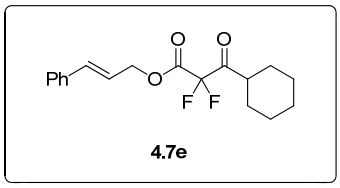


4.9d

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

General procedure F was followed using **4.7d** (76.5 mg, 0.200 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), PhXPhos (9.3 mg, 0.020 mmol), and 1,4-dioxane (2.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.9d** as a colorless solid (49 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1 H), 8.16 (s, 1 H), 7.67 (dt, *J* = 8.4, 1.9 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.42–7.25 (m, 6 H), 6.25 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1 H), 5.35 (d, *J* = 10.4 Hz, 1 H), 5.29 (dt, *J* = 16.8, 1.2 Hz, 1 H), 4.28 (td, *J* = 16.4, 8.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.8 (t, *J* = 31.2 Hz), 143.0 (t, *J* = 3.1 Hz), 139.1, 135.2 (d, *J* = 5.0 Hz), 132.2 (dd, *J* = 4.4, 3.1 Hz), 131.4 (t, *J* = 5.6 Hz), 129.9, 129.8,

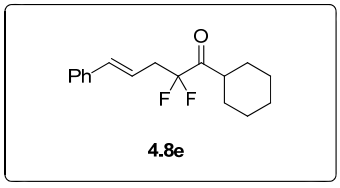
128.8, 128.3, 128.2, 121.0, 120.4, 120.1, 118.6 (t, J = 255.6 Hz), 53.8 (t, J = 22.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.6 (dd, A of ABX, J_{AB} = 263.2 Hz, J_{AX} = 15.0 Hz, 1 F), –106.2 (dd, B of ABX, J_{AB} = 263.2 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 3065, 3032, 1684, 1599, 1541, 1504, 1250, 1174, 1036, 951, 887, 758, 725, 700, 688, 658 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{17}F_2N_2O$ $[M+H]^+$ 339.1309, found 339.1303. mp 81–82 °C.



4.7e

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

General procedure D was followed using potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate[3] (1.5 g, 6.1 mmol), oxalyl chloride (0.52 mL, 6.1 mmol), cinnamyl alcohol (1.1 g, 8.0 mmol), Et_3N (1.0 mL, 7.4 mmol), DMF (1.0 mL), and CH_2Cl_2 (20 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **4.7e** as a colorless oil (1.6 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.40 (m, 2 H), 7.37–7.30 (m, 3 H), 6.73 (d, J = 15.6 Hz, 1 H), 6.27 (dt, J = 15.6, 6.8 Hz, 1 H), 4.95 (d, J = 6.8 Hz, 2 H), 2.95–2.89 (m, 1 H), 1.94–1.89 (m, 2 H), 1.83–1.78 (m, 2 H), 1.71–1.68 (m, 1 H), 1.47–1.17 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.3 (t, J = 26.9 Hz), 161.7 (t, J = 30.6 Hz), 136.6, 135.8, 128.9, 128.8, 127.0, 120.9, 108.8 (t, J = 263.8 Hz), 68.1, 45.5, 28.3, 25.6, 25.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –112.9 (s, 2 F). IR (film) 2935, 2858, 1776, 1736, 1450, 1310, 1202, 1144, 966, 746, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{20}F_2O_3Na$ $[M+Na]^+$ 345.1278, found 345.1284.

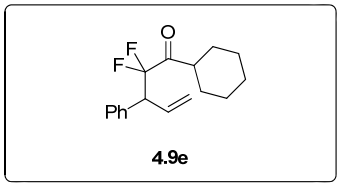


4.8e

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

General procedure E was followed using **4.7e** (96.7 mg, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), *t*-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). The reaction was run at 70 °C, and the

reaction time was extended to 36 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.8e** as a light yellow oil (51.0 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.23 (m, 5 H), 6.54 (d, *J* = 16.0 Hz, 1 H), 6.08 (dt, *J* = 16.0, 7.4 Hz, 1 H), 2.98–2.86 (m, 3 H), 1.88–1.77 (m, 4 H), 1.71–1.67 (m, 1 H), 1.42–1.19 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.3 (t, *J* = 29.4 Hz), 136.8, 136.5, 128.8, 128.0, 126.5, 118.8 (t, *J* = 5.6 Hz), 118.0 (t, *J* =253.1 Hz), 45.1, 37.2 (t, *J* = 23.8 Hz), 28.3, 25.8, 25.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –105.6 (t, *J* = 16.9 Hz, 2 F). IR (film) 2934, 2856, 1734, 1497, 1450, 1207, 1146, 1057, 1032, 968, 748, 692 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{20}F_2ONa$ $[M+Na]^+$ 301.1380, found 301.1388.

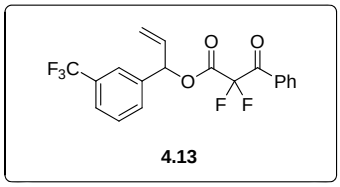


4.9e

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

General procedure F was followed using **4.7e** (96.7 mg, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), PhXPhos (13.9 mg, 0.0300 mmol), and 1,4-dioxane (3.0 mL). The reaction time was extended to 36 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **4.9e** as a light yellow oil (61.0 mg, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.28 (m, 5 H), 6.17 (ddd, *J* = 17.2, 10.0, 8.4 Hz, 1 H), 5.32 (d, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 17.2 Hz, 1 H), 4.16–4.05 (m, 1 H), 2.63–2.56 (m, 1 H), 1.78–1.74 (m, 2 H), 1.68–1.62 (m, 2 H), 1.44–1.39 (m,1 H), 1.28–1.08 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.0 (t, *J* = 28.8 Hz), 135.2 (d, *J* = 5.0 Hz), 132.4 (dd, *J* = 6.2, 2.5 Hz), 129.8, 128.8, 128.1, 120.8, 118.1 (t, *J* = 258.1 Hz), 53.1 (t, *J* = 21.9 Hz), 45.9, 28.1, 27.7, 25.7, 25.6, 25.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –112.0 (dd, A of AMX, J_{AM} = 263.2 Hz, J_{AX} = 16.9 Hz, 1 F), –107.6 (dd, M of AMX, J_{AM} = 263.2 Hz, J_{MX} = 15.0 Hz, 1 F). IR (film) 2934, 2856, 1732, 1494, 1452, 1207, 1167, 1059, 1032, 966, 930, 742, 700 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{20}F_2ONa$ $[M+Na]^+$ 301.1380, found 301.1378.

Preparation of Compound 4.13 in Scheme 4.13B



4.13

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

An oven-dried one-neck round-bottom flask was charged with potassium salt potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[3] (1.0 g, 4.2 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (21 mL) and DMF (0.10 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.31 mL, 3.7 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2 h. Next, a solution of 1-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol[15] (0.71 g, 3.5 mmol) dissolved in dry CH_2Cl_2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et_3N (0.97 mL, 7.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2 h. H_2O (10 mL) was added to quench the reaction, and the CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (0% to 15% EtOAc in hexanes) afforded the title compound **4.13** as a colorless oil (0.81 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (dd, *J* = 8.0, 1.4 Hz, 2 H), 7.69–7.65 (m, 1 H), 7.59 (dt, *J* = 6.4, 1.8 Hz, 1 H), 7.54–7.47 (m, 5 H), 6.45 (d, *J* = 6.0 Hz, 1 H), 5.98 (ddd, *J* = 17.0, 10.8, 6.2 Hz, 1 H), 5.42–5.40 (m, 1 H), 5.37 (d, *J* = 1.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.0 (t, *J* = 30.6 Hz), 138.0, 135.4, 133.7, 131.3 (q, *J* = 32.5 Hz), 131.1, 130.7, 130.1 (t, *J* = 3.1 Hz), 129.5, 129.2, 125.8 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 270.9 Hz), 119.9, 109.9 (t, *J* = 263.7 Hz), 79.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.5 (d, A of AB, *J* = 289.5 Hz, 1 F), –107.1 (d, B of AB, *J* = 289.5 Hz, 1 F), –62.7 (s, 3 F). IR (film) 3072, 1778, 1714, 1699, 1599, 1452, 1333, 1256, 1167, 1128, 1074, 926, 804, 704, 687, 580 cm^{-1}. HRMS (EI, *m/z*): calcd for $C_{19}H_{12}F_5O_3$ [M–H$^+$] 383.0707, found 383.0698.

Experimental Procedures for Catalytic Reactions in Scheme 4.13B

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

Experimental Procedures for Catalytic Reactions in the Presence of Acidic Additives

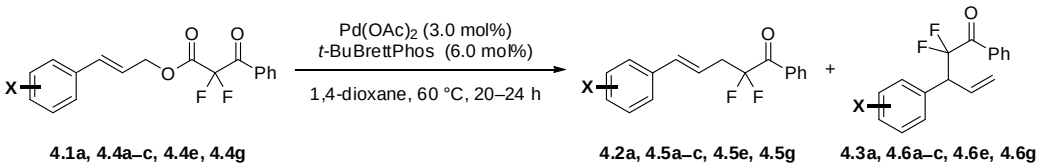
Entry 2 in Scheme 15: An oven-dried 1 dram vial A was charged with $Pd(OAc)_2$ (2.0 mg, 0.0090 mmol), *t*-BuBrettPhos (8.7 mg, 0.018 mmol), and a magnetic stir bar. The vial A was equipped with a three-way valve, and evacuated and backfilled with $N_{2(g)}$ three times. Dry 1,4-dioxane (0.2 mL) was added *via* a syringe under $N_{2(g)}$. The vial was sealed with PTFE-lined silicone septa under $N_{2(g)}$, and the mixture was stirred at 80 °C for 10 min (pre-activation), and then cooled to rt. Subsequently, another oven-dried vial B was charged with a magnetic stir bar, the substrate **4.1a** (0.300 mmol) and acetyl acetone (30 μL, 0.300 mmol), and the dry1,4-dioxane (0.3 mL) was added *via* a syringe under $N_{2(g)}$, and stirred at rt thoroughly. The solution in the vial B was transferred to the vial A *via* a syringe under $N_{2(g)}$, and another dry1,4-dioxane (0.1 mL) was used to wash inner wall of the vial B and the solution was transferred to the vial A again. The vial A was stirred at rt for 5 min, and then placed on a pre-heated reaction block at 60 °C, and

stirred for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). α,α,α-Trifluorotoluene (15 μL, 0.12 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial A for ^{19}F NMR analysis to determine the ratio of fluorinated products **4.2a**, **4.3a**, and **4.3a′**. After determination of the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. The solvents were removed under reduced pressure, and ^{1}H NMR of the crude mixture was analyzed for determining the ratio of allylated products **4.2a′** based on the integration related to **4.2a**.

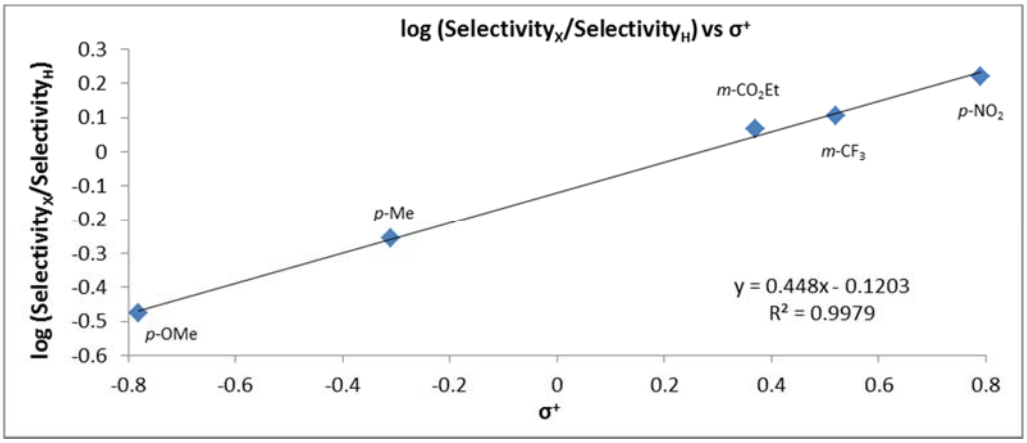
Entry 4 in Scheme 15: An oven-dried 1 dram vial A was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.0150 mmol) and a magnetic stir bar. The vial A was equipped with a three-way valve, and evacuated and backfilled with $N_{2(g)}$ three times. Dry 1,4-dioxane (1.0 mL) was added *via* a syringe under $N_{2(g)}$. The vial was sealed with PTFE-lined silicone septa under $N_{2(g)}$, and the mixture was stirred at 80 °C for 10 min (pre-activation), and then cooled to rt. Subsequently, another oven-dried vial B was charged with a magnetic stir bar, the substrate **4.1a** (0.300 mmol) and acetyl acetone (30 μL, 0.300 mmol), and the dry1,4-dioxane (1.5 mL) was added *via* a syringe under $N_{2(g)}$, and stirred at rt thoroughly. The solution in the vial B was transferred to the vial A *via* a syringe under $N_{2(g)}$, and another dry1,4-dioxane (0.5 mL) was used to wash inner wall of the vial B and the solution was transferred to the vial A again. The vial A was stirred at rt for 5 min, and then placed on a pre-heated reaction block at 90 °C, and stirred for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.5 mL). α,α,α-Trifluorotoluene (15 μL, 0.12 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial A for ^{19}F NMR analysis to determine the ratio of fluorinated products **4.2a**, **4.3a**, and **4.3a′**. After determination of the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. The solvents were removed under reduced pressure,

and ^{1}H NMR of the crude mixture was analyzed for determining the ratio of allylated products **4.2a′** based on the integration related to **4.3a**.

Analysis of Selectivity Data in Figures 1 and 2

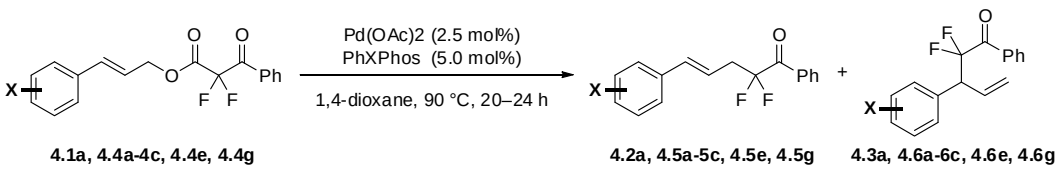


4.1a, 4.4a–c, 4.4e, 4.4g **4.2a, 4.5a–c, 4.5e, 4.5g** **4.3a, 4.6a–c, 4.6e, 4.6g**

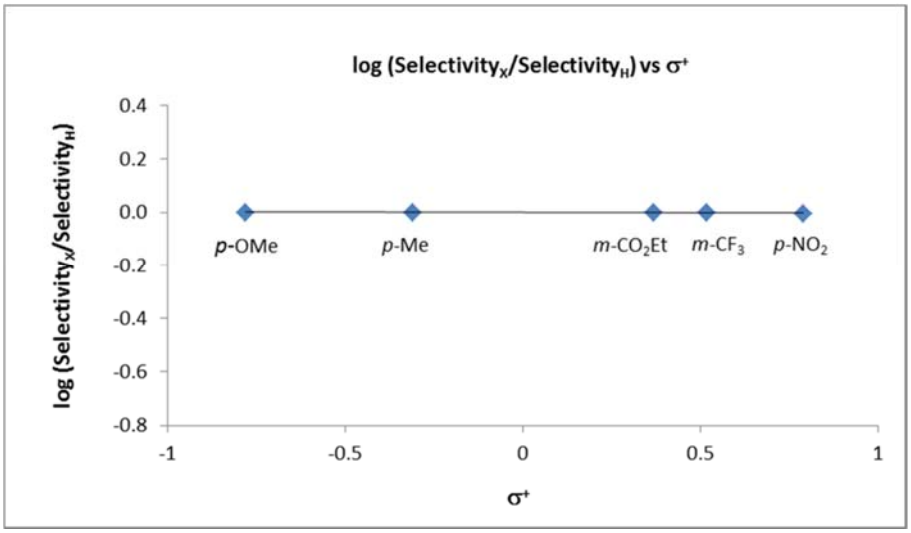


Substrate	Substituent (X)	Selectivity (lin/br)	Log (Selectivity$_X$/ Selectivity$_H$)	σ$^+$
1a	H	18	–	–
4a	*m*-CF_3	23	0.1065	0.52
4b	*p*-NO_2	30	0.2218	0.79
4c	*m*-CO_2Et	21	0.0669	0.37
4e	*p*-Me	10	0.2553	–0.31
4g	*p*-OMe	6	0.4771	–0.78

Values for σ$^+$ were obtained from the literature.[16]



4.1a, 4.4a-4c, 4.4e, 4.4g **4.2a, 4.5a-5c, 4.5e, 4.5g** **4.3a, 4.6a-6c, 4.6e, 4.6g**



Substrate	Substituent (X)	Selectivity (br/lin)	Log (Selectivity$_X$/ Selectivity$_H$)	σ^+
1a	H	99	–	–
4a	*m*-CF_3	99	0.0000	0.52
4b	*p*-NO_2	98	-0.0004	0.79
4c	*m*-CO_2Et	99	0.0000	0.37
4e	*p*-Me	99	0.0000	–0.31
4g	*p*-OMe	99	0.0000	–0.78

References for Chapter 4 Experimental Section

[1] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. "Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure" *J. Am. Chem. Soc*. **2005**, *127*, 4685–4696.
[2] Hoshiya, N.; Buchwald, S. L. "An Improved Synthesis of BrettPhos- and RockPhos-Type Biarylphosphine Ligands" *Adv. Synth. Catal*. **2012**, *354*, 2031–2037.
[3] Yang, M.-H.; Orsi, D. L.; Altman, R. A. "Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation Reaction to Access α,α-Difluoroketones" *Angew. Chem., Int. Ed*. **2015**, *54*, 2361–2365.
[4] Gilbert, J. C.; Kelly, T. A. "Transesterification of 3-Oxo Esters with Allylic Alcohols" *J. Org. Chem*. **1988**, *53*, 449–450.
[5] He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L. "Ir-Catalyzed Regio- and Enantioselective Decarboxylative Allylic Alkylations" *Org. Lett*. **2007**, *9*, 4339–4341.
[6] Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. "Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of β-Ketoesters" *Org. Lett*. **2003**, *5*, 1709–1712.
[7] Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. "Highly Controlled Chemoselectivity of Tin Enolate by Its Hybridization State. Anionic Complex of Tin Enolate Coordinated by Tetrabutylammonium Bromide as Halo Selective Reagent" *J. Am. Chem. Soc*. **1998**, *120*, 715–721.
[8] Evans, P. A.; Leahy, D. K. "Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Alkylation Reactions Using Copper(I) Enolates: Synthesis of (-)-Sugiresinol Dimethyl Ether" *J. Am. Chem. Soc*. **2003**, *125*, 8974–8975.
[9] Ambler, B. R.; Altman, R. A. "Copper-Catalyzed Decarboxylative Trifluoromethylation of Allylic Bromodifluoroacetates" *Org. Lett*. **2013**, *15*, 5578–5581.
[10] Jeffery, T. "Palladium-Catalyzed Arylation of Allylic Alcohols: Highly Selective Synthesis of β-Aromatic Carbonyl Compounds or β-aromatic α,β-Unsaturated Alcohols" *Tetrahedron Lett*. **1991**, *32*, 2121–2124.
[11] Hatsuda, M.; Kuroda, T.; Seki, M. "An Improved Synthesis of (*E*)-Cinnamic Acid Derivatives *via* the Claisen-Schmidt Condensation" *Synthetic Communications*, **2003**, *33*, 427–434.
[12] Loelsberg, W.; Ye, S.; Schmalz, H.-G. "Enantioselective Copper-Catalysed Allylic Alkylation of Cinnamyl Chlorides by Grignard Reagents Using Chiral Phosphine-Phosphite Ligands" *Adv. Synth. Catal*. **2010**, *352*, 2023–2031.
[13] Angle, S. R.; Choi, I.; Tham, F. S. "Stereoselective Synthesis of 3-Alkyl-2-aryltetrahydrofuran-4-ols: Total Synthesis of (±)-Paulownin" *J. Org. Chem*. **2008**, *73*, 6268–6278.
[14] Charette, A. B.; Molinaro, C.; Brochu, C. "Catalytic Asymmetric Cyclopropanation of Allylic Alcohols with Titanium-TADDOLate: Scope of the Cyclopropanation Reaction" *J. Am. Chem. Soc*. **2001**, *123*, 12168–12175.
[15] 1-(3-(Trifluoromethyl)phenyl)prop-2-en-1-ol was prepared according to the procedure described in the following patent: O. Thiel, C. Bernard, R. Larsen, M. J. Martinelli, M. T. Raza (Amgen Inc., USA), 2009002427, **2008**.
[16] Brown, H. C.; Okamoto, Y. "Derective Effects in Aromatic Substitution. XXX. Electrophilic Substituent Constants" *J. Am. Chem. Soc*. **1958**, *80*, 4979–4987.

Chapter 5. Palladium-Catalyzed *para*-C–H Difluoroalkylation of Arenes *via* Decarboxylation of Benzyl α,α-Difluoro-β-keto-esters

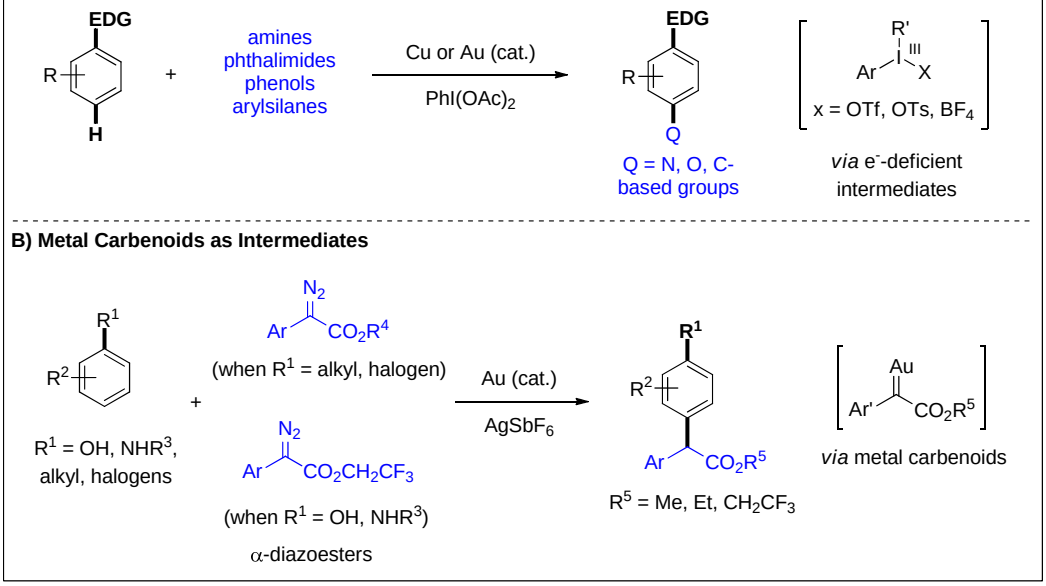
5.1 Introduction to Selective para-C–H Functionalization of Arenes

The functionalization of C–H bonds represents an important and powerful strategy for converting simple arenes and hydrocarbons to more complex molecules.[1] This strategy mainly utilizes transition metals to functionalize inert C–H bonds, and react them with carbon- and heteroatom-based reagents to generate coupling products.[2] The C–H functionalization strategy avoids the use of pre-functionalized precursors, thus provides an atom-economic and time-saving transformation for building structurally complicated natural products, especially for late-stage modifications of bioactive molecules.[3] Moreover, the C–H functionalization method enables distinct bond disconnections in retrosynthetic analysis of natural products, which could create new and efficient synthetic strategies.[3b–d] However, the reliability and value of such a C–H functionalization reaction depend on chemoselective activation of one C–H bond over others. To address selectivity issues, many methods have been developed to activate a specific C–H bond.[4] For aromatic systems, the utilization of auxiliary groups and well-designed transition-metal catalysts has enabled selective *ortho*-,[5] and even *meta*[6]-C–H functionalization of arenes.

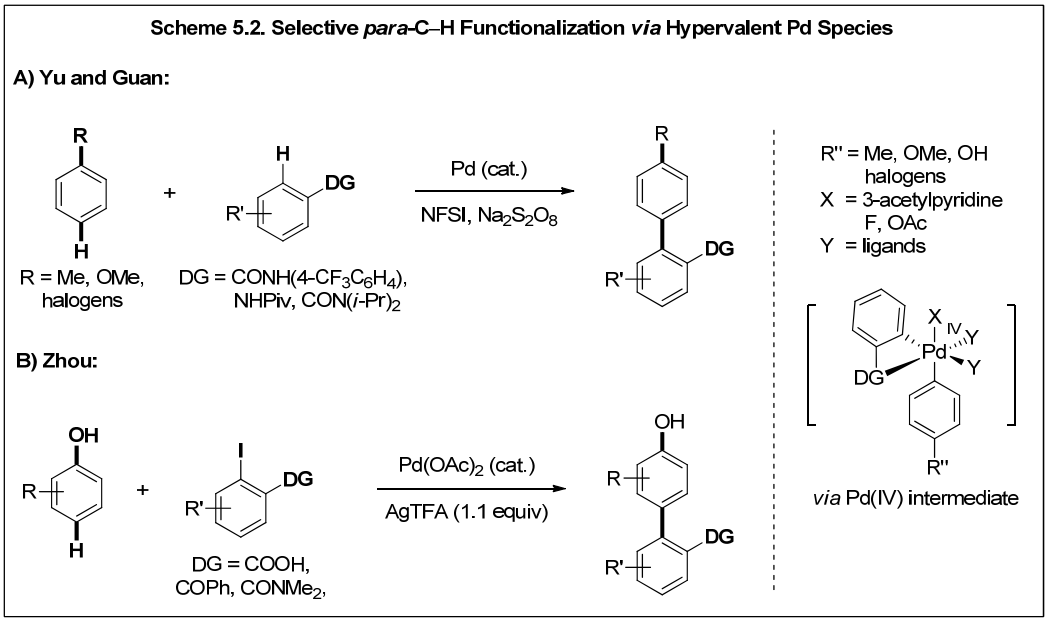
However, the strategies to selectively activate C–H bonds at the *para*-position of arenes remain limited. Current methods for *para*-C–H functionalization reactions mainly utilize electronic control of substrates. In this strategy, arenes couple with *in situ* generated electrophilic intermediates, including iodonium salts or metal carbenoids, to generate *para*-functionalized arenes (Scheme 5.1). In the case of iodonium salts as reactive intermediates,[7] electron-rich arenes proceeded much more quickly than electron-deficient arenes, most of which did not participate in the reactions (Scheme 5.1A). This result supported the assertion that the reactions proceeded by an electrophilic aromatic substitution or metalation (S_EAr or EAM) mechanism, thus only tolerating electron-rich aromatic substrates. For the reactions that proceed through electrophilic gold carbenoids,[8] more electron-deficient fluorinated α-

diazoester precursors were required to facilitate reactions of the substrates bearing alkyl- and halogen-substituted arenes (Scheme 5.1B).

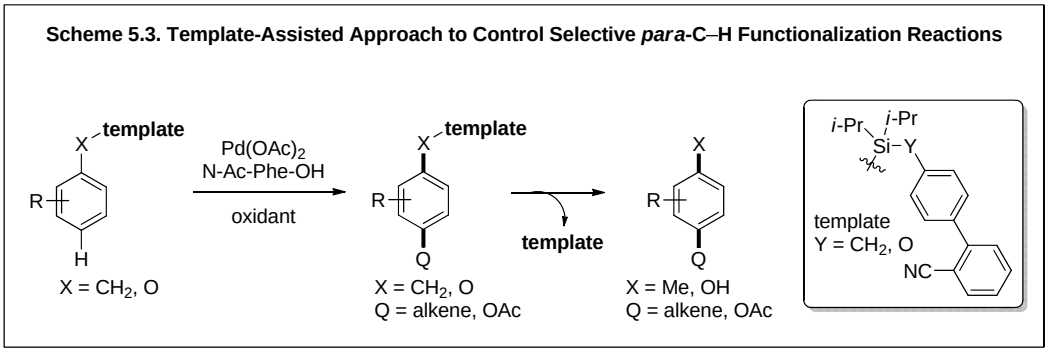
Scheme 5.1. Electronic Control of Substrates on Selective *para*-C–H Functionalization Reactions



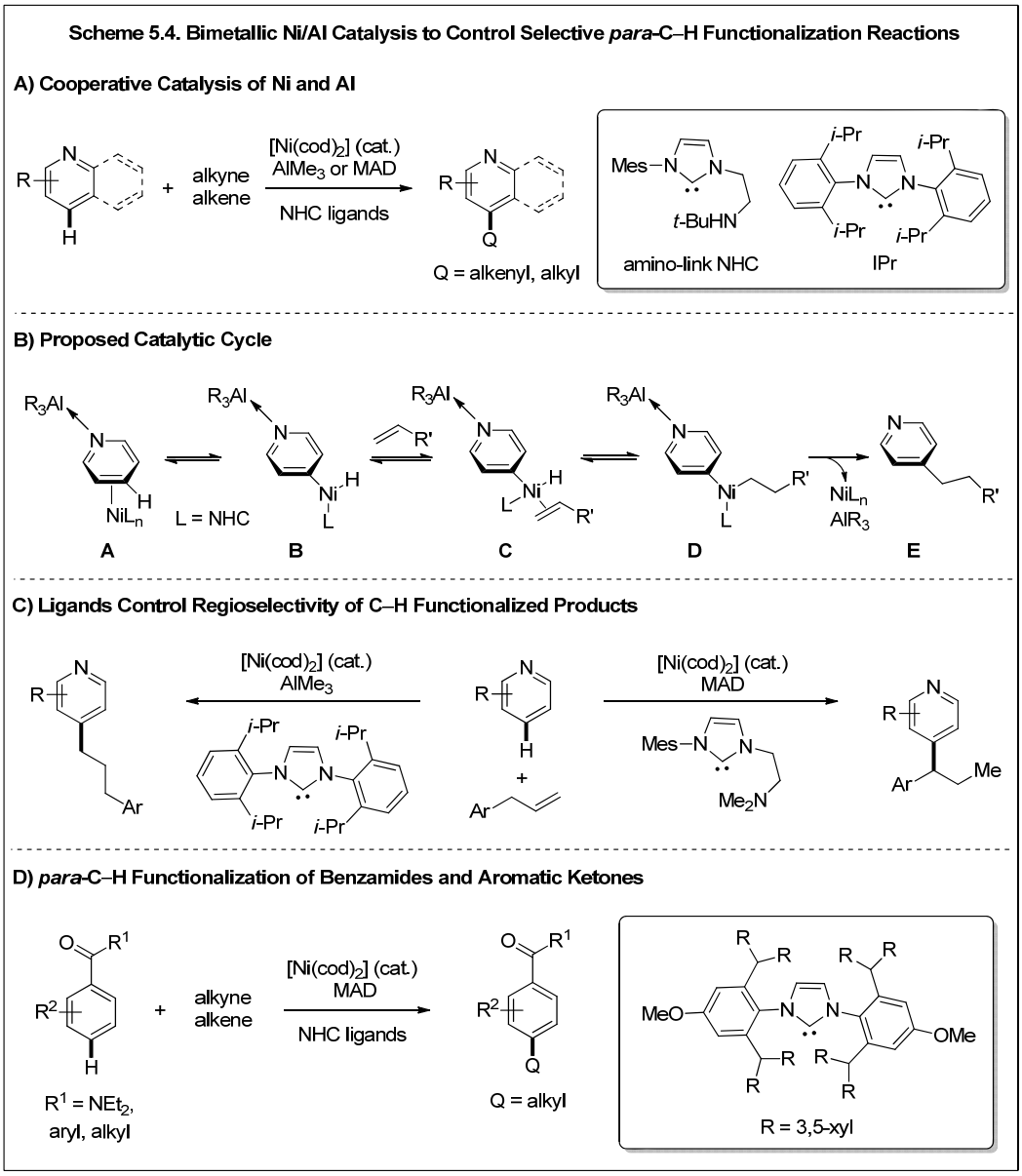
Moreover, the combination use of electron-rich arenes with palladium catalysts under oxidative conditions provided an alternative strategy for accessing *para*-biphenyl derivatives (Scheme 5.2). The Yu group proposed that this method contains two C–H activation steps (Scheme 5.2A).[9a–c] First, the directing group (DG) on one aromatic ring facilitated the formation of a cyclopalladated Pd(II) complex, which was oxidized to a Pd(IV) species by oxidants. Then, the ligand/directing group-stabilized Pd(IV) species could undergo an electrophilic palladation of electron-rich arenes, followed by reductive elimination, to generate *para*-functionalized products. In the reactions, the Yu group also utilized 3-acetylpyridine as a ligand that coordinates to Pd(IV) center to facilitate electrophilic palladation, and avoided the use of stoichiometric amount of oxidant NFSI. Similarly, the Zhou lab also proposed a Pd(II)/Pd(IV) catalytic cycle for the reactions of phenol derivatives with aryl iodides (Scheme 5.2B).[9d] Despite these reactions provided *para*-functionalized products in high selectivity, they required the use of stoichiometric amount of oxidants, and directing group-containing aromatic systems, both of which caused organic wastes and narrowed the substrate scope.



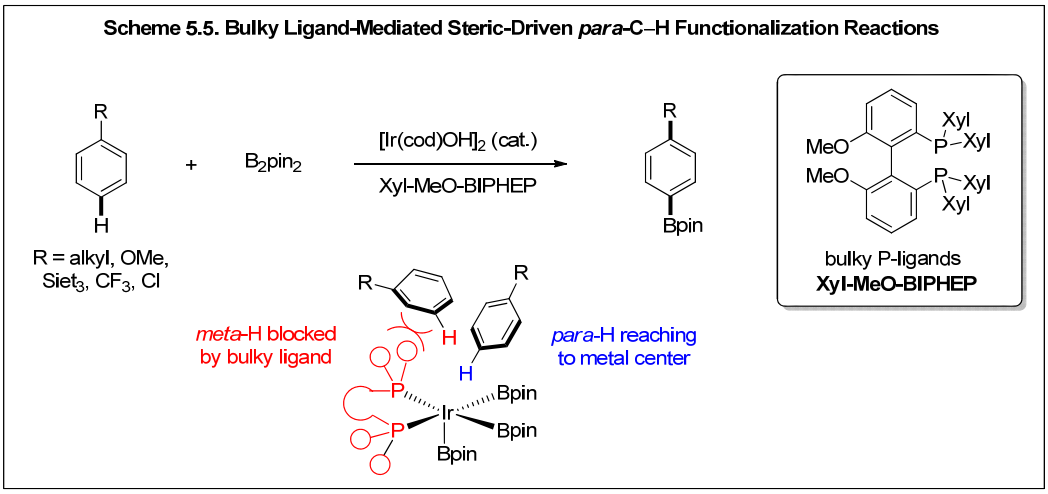
The auxiliary group-based approach presents difficulty in *para*-C–H transformations, because of the challenge of designing a directing group with appropriate length to reach the distal C–H bond, activate it, and form a pre-organized metallacycle for reactions. Recently, a silyl biphenyl-based template enabled for selective *para*-C–H functionalization of toluene and phenol derivatives (Scheme 5.3).[10] However, this method requires the pre-installation of the template to the substrates through an appropriate functional group for attachment, and the removal of the heavy template at a late stage, which narrows the substrate scope and adds extra synthetic steps, respectively.



To overcome these limitations, the strategies that use transition-metal catalysts to control *para*-selectivity enables the activation of C–H bonds at the *para*-position of heterocycles and electron-deficient arenes. For example, the Ong and Hiyama labs utilized a Ni/Al bimetallic catalyst system to activate the *para*-C–H bond of pyridines and quinolones (Scheme 5.4A).[11a,b] The combination of Ni/Al catalysts enabled the formation of a reactive species **A**, in which Ni σ-bonds to two NHC ligands and η^2-bonds to the pyridine with the nitrogen atom coordinating to Al, and directed the metalation to occur at the more acidic and less sterically congested *para*-position of pyridine to form the Ni(II) complex **B**. Subsequently, coordination of alkenes to the complex **B**, followed by migratory insertion into Ni–H bond generated the intermediate **D**, which underwent reductive elimination to provide the coupling product and regenerate Ni(0) to close the catalytic cycle (Scheme 5.4B).[11b] Moreover, the use of structurally distinct ligands enabled the regioselective formation of linear and branched products, thus extending reaction pattern (Scheme 5.4C).[11c] Recently, the Nakao group combined a bulky Ni/Al cocatalyst with a bulky NHC ligand to develop a powerful catalytic system that can functionalize the *para*-C–H bond of electron-deficient arenes, such as benzamides and aromatic ketones (Scheme 5.4D).[11d] In the reaction mode, the interaction of aluminum Lewis acid with the carbonyl group electronically enhanced the reactivity of the *para*-C–H bond toward an electron-rich Ni center, and a steric repulsion between the bulky Al center and the bulky ligand pushed the Ni catalyst to the *para*-C–H bond. The cooperation of the electronic and steric effects significantly improved the yields and selectivity compared to previous reports.

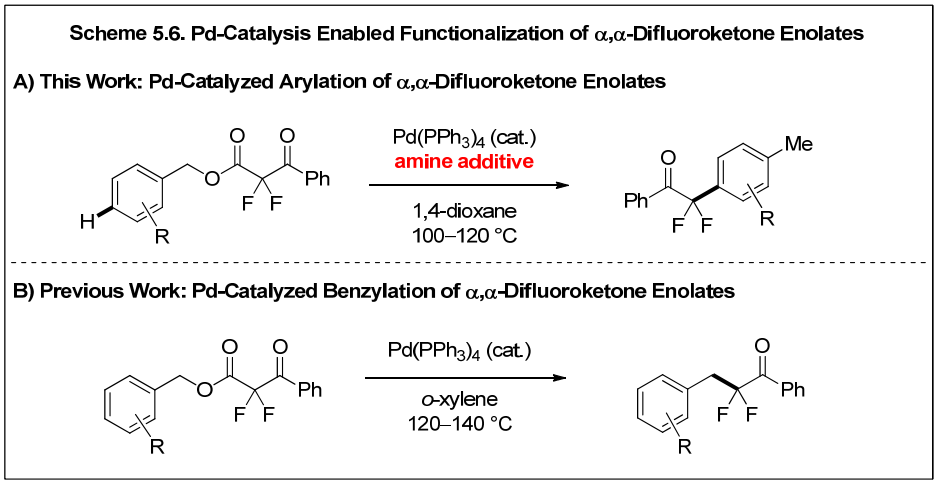


Additionally, the Itami group developed an iridium catalyst bearing a bulky ligand to undergo *para* selective borylation (Scheme 5.5).[11e] This *para*-selectivity derived from a steric repulsion between the substrate and bulky ligand of the catalyst, which prevented *meta*-H from approaching the metal center, and inhibited its activation. The strategy utilizing bulky catalyst to drive *para*-selectivity enabled to functionalize electron-deficient arenes, which are challenging substrates to functionalize by alternative methods.



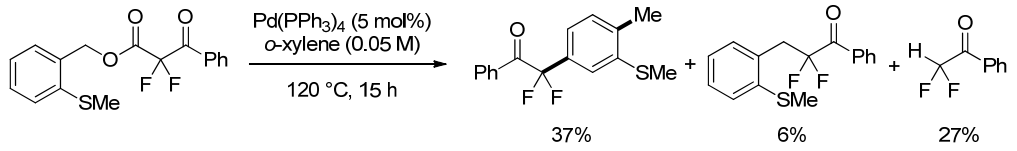
5.2 Base-Promoted Selective para-Difluoroalkylation of Arenes

To complement these known strategies, we report a base-mediated *para*-C–H difluoroalkylation of arenes using palladium catalysis (Scheme 5.6). In this reaction, amine additives play an essential role in promoting a C–H functionalization pathway (Scheme 5.6A) and disfavoring a traditional decarboxylative benzylation reaction (Scheme 5.6B).[12] This reaction represents the unique example in which a base can switch the selectivity from cross-coupling to C–H functionalization.



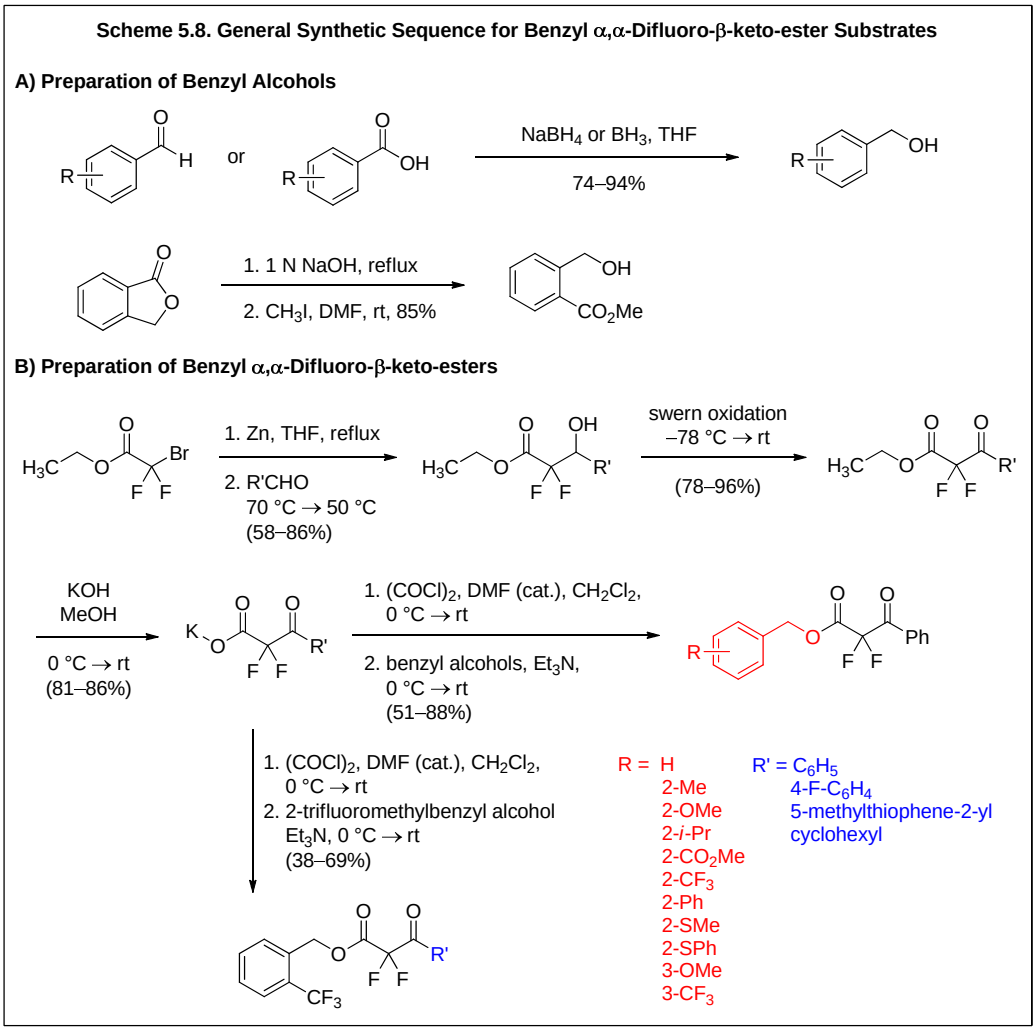
The formation of such a α-aryl-α,α-difluoroketone was initially observed as a side product during the exploration of the substrate scope in the decarboxylative benzylation of α,α-difluoroketone enolates. We found that the reaction of *ortho*-thio-substituted benzyl substrates generated the desired α-benzyl-α,α-difluoroketone product together with the unexpected α-aryl-α,α-difluoroketone (Scheme 5.7). After the isolation and 2D NMR analysis of the α-aryl-α,α-difluoroketone product, it was concluded that the α,α-difluoroketone moiety was incorporated at the *para*-position of arenes relative to the methyl group.

Scheme 5.7. Formation of α-Aryl-α,α-difluoroketones under Benzylation Condition



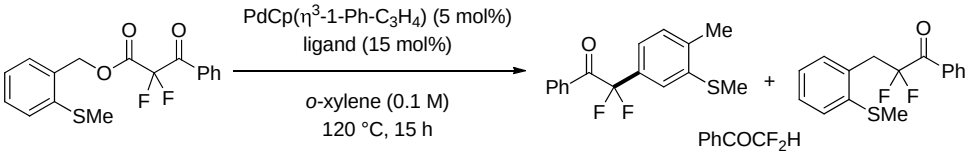
Although α-aryl-α,α-difluoroketones can be accessed by known methods, its formation *via* a decarboxylative C–H functionalization reaction has not been reported. Thus, we aimed to develop a selective C–H functionalization method for accessing α-aryl-α,α-difluoroketones. To begin the study, a variety of *ortho*- and *meta*-substituted benzyl α,α-difluoro-β-keto-esters were identified as potential substrates, and they were prepared through four steps, including 1) Reformatsky addition of ethyl bromodifluoroacetate to aldehydes; 2) oxidation of alcohols to ketones; 3) basic hydrolysis of ethyl esters; and 4) esterification of β-keto-α,α-difluoroacetate with substituted benzyl alcohols (Scheme 5.8).[12]

Scheme 5.8. General Synthetic Sequence for Benzyl α,α-Difluoro-β-keto-ester Substrates



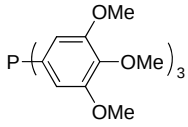
Initial screening focused on the identification of appropriate ligands that can promote *para*-C–H arylation reaction, and suppress cross-coupling benzylation reaction (Table 5.1). Generally, electron-deficient ligands (entry 1) caused low conversion, and inhibited the arylation reaction, while more electron-rich ligands benefited the arylation reaction, and provided the arylated product in about 30% yields (entries 2–5). However, ligands that were excessively electron-rich (entry 6), hindered, and bidentate suppressed the catalytic C–H arylation reaction.

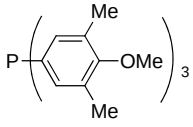
Table 5.1. Electron-Rich Triphenylphosphine Ligands Favored Formation of Arylated Product

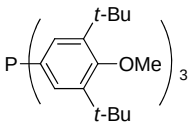


entry	ligand	arylation (%)	benzylation (%)	$PhCOCF_2H$ (%)	conv. (%)
1	$P(4\text{-}CF_3C_6H_4)_3$	4	1	2	15
2	PPh_3	33	2	22	88
3	$PPh_2(4\text{-}OMeC_6H_4)$	35	2	27	93
4	$PPh(4\text{-}OMeC_6H_4)_2$	32	2	29	92
5	$P(4\text{-}OMeC_6H_4)_3$	30	1	32	93
6	$P(4\text{-}NMe_2C_6H_4)_3$	0	0	17	37

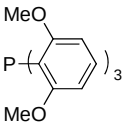
Other ligands screened that produced < 25% arylated product by ^{19}F NMR analysis were shown below.

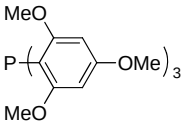


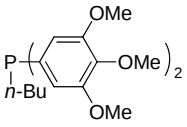




Xantphos
DPEPhos
t-BuXantphos
rac-BINAP
dppBz
dppe
dppp
dppf







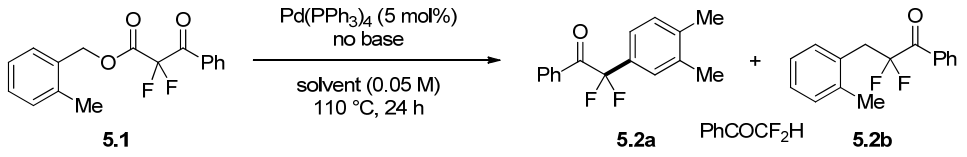
PCy_3
$P(t\text{-}Bu)_3$
tri(2-furyl)phosphine
$P(4\text{-}MeC_6H_4)_3$
$P(4\text{-}PhC_6H_4)_3$
$P(2\text{-}OMeC_6H_4)_3$

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

Since S-containing groups can also serve as a ligand and coordinate to palladium that could interfere with a catalyst system and deactivate the palladium catalyst, we used another substrate (**5.1**) bearing a non-coordinating group for screening. During the optimization, we found that electronic properties of ligands and palladium catalysts or precatalysts affected the selectivity of arylation to benzylation products; however, no obvious trend was observed. For example, the catalyst system of $PdCp(\eta^3\text{-}C_3H_4)/P(4\text{-}OMeC_6H_4)_3$ favored the arylated product, while the catalyst system of $Pd(dba)_2/P(4\text{-}OMeC_6H_4)_3$ still preferred the benzylated product. For these conditions, the yield of arylated product **5.2a** was less than 40%. To further improve the yield, solvent screening was performed. Interestingly, the distribution of products closely correlated with the solvent used (Table 5.2). Specifically, hydrocarbon and ether solvents provided benzylated product **5.2b** (entries 1–4), while polar and coordinating solvents favored arylated

product **5.2a** (entries 5–8). Although full conversion was achieved for these conditions, the yield of arylated product **5.2a** did not increase further.

Table 5.2. Solvents Affected Selectivity between Benzylation and Arylation[a,b]



5.1 **5.2a** $PhCOCF_2H$ **5.2b**

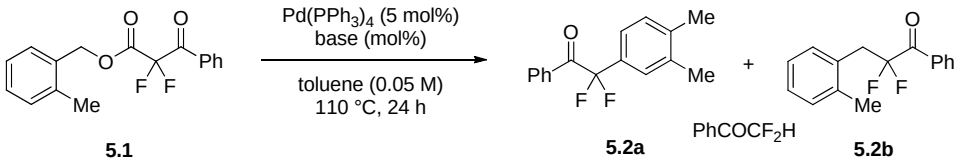
entry	solvent	**5.2a** (%)	**5.2b** (%)	$PhCOCF_2H$ (%)
1	o-xylene	0	97	2
2	1,4-dioxane	0	quant.	0
3	anisole	0	quant.	0
4	diglyme	2	87	4
5	butyronitrile	42	7	25
6	DMA	45	8	25
7	DMF	47	8	27
8	DMSO	24	6	50

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.
[b] Full conversion was observed except for entry 4 (conv. 97%)

Amine additives could favor the *para*-selective C–H arylation reaction. Considering that a dearomatization-rearomatization process might operate in the catalytic arylation reaction of α,α-difluoroketone enolates, we explored the use of bases that could facilitate the rearomatization step and enhance the yields. Interestingly, the strength of bases affected the selectivity of arylation to benzylation (Table 5.3). Nitriles, inorganic bases, and weak bases, such as pyridine and anilines, exclusively provided the benzylated product **5.2b** (entries 2–7). In contrast, more basic amines, including *N*,*N*-dimethylaminopyridine (DMAP), tripropylamine (*n*-Pr_3N), triethylamine (Et_3N), and the chelating base (TMEDA) gave the arylated product **5.2a** (entries 8–11). Further exploration of aliphatic amines demonstrated correlation between rigidity/hindrance and selectivity. The conformationally constrained base quinuclidine provided low yield of arylated product **5.2a** (entry 12), while the bulky diisopropylethyl amine (DIPEA) favored the benzylated product **5.2b** (entry 13). Thus, Et_3N with a compromise between basicity and steric hindrance generated the arylated product **5.2a** in the highest yield (entries 10). Additionally, the stoichiometry of Et_3N also influenced the yield of arylated product **5.2a**. Increased

amount of Et_3N improved the selectivity towards the arylated product **5.2a** (entries 10, and 14–16), but more than 1 equivalent of Et_3N did not increase the yield (entries 10 and 17). After further optimization, the final conditions [2.5 mol% of $Pd(PPh_3)_4$/1.0 equiv of Et_3N/1,4-dioxane/100 °C] provided the desired arylated product **5.2a** in 75% isolated yield (entry 18), thus manifesting the importance of Et_3N on the *para*-selective C–H difluoroalkylation of arenes.

Table 5.3. Bases Remarkably Affected Selectivity between Benzylation and Arylation[a,b]



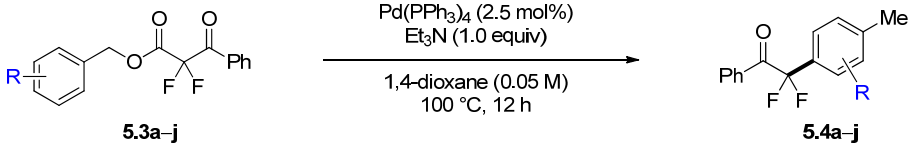
5.1 **5.2a** **5.2b**

entry	base (mol%)	**5.2a** (%)	**5.2b** (%)	$PhCOCF_2H$ (%)
1	-	0	89	0
2	butyronitrile (300)	0	88	3
3	Na_2CO_3 (300)	0	91	3
4	PhONa (100)	0	0	18
5	$PhCO_2K$ (100)	2	71	6
6	pyridine (100)	4	85	0
7	*N*, *N*-dimethylaniline (100)	0	89	2
8	DMAP (100)	54	4	17
9	N(*n*-Pr)$_3$ (100)	58	13	6
10	Et_3N (100)	70	5	6
11	TMEDA (100)	69	5	8
12	quinuclidine (100)	12	1	10
13	DIPEA (100)	12	68	4
14	Et_3N (50)	65	7	5
15	Et_3N (25)	63	11	5
16	Et_3N (10)	49	26	4
17	Et_3N (300)	69	5	5
18[c]	Et_3N (100)	82 (75)	7	6

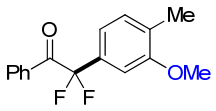
[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.
[b] Full conversion was observed.
[c] The optimized conditions: **5.1** (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), Et_3N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. ^{19}F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs)

A variety of substrates bearing distinct electronic properties and substituent patterns on benzylic moieties underwent the decarboxylative arylation to incorporate a α,α-difluoroketone moiety at the *para*-position of arenes relative to the methyl group (Table 5.4). Generally, *ortho*-substituted electron-rich (**5.3a**–**b**) and -deficient (**5.3c**–**d**) substrates provided the arylated products (**5.4a**–**d**) in modest to high yields. Particularly, in the case of the substrate **5.3d**, no benzylated product was observed by ^{19}F NMR. The reaction of the substrate (**5.3e**) bearing a bulky phenyl group on the *ortho*-posotion of the aromatic ring gave the product (**5.4e**) in modest yield. In this reaction of the substrates **5.3e**, we isolated 35% of the major side product, 9*H*-fluorene, which might come from an intramolecular cyclization reaction. Moreover, substrates bearing a coordinating group (**5.3f**–**g**) at the *ortho*-positions tolerated the present reaction and produced the arylated products (**5.4f**–**g**) in good yields and selectivity using higher catalyst loading and increasing reaction temperatures. Even a non-substituted simple benzyl substrate (**5.3h**) was transformed to the arylated product (**5.4h**) in modest yield and selectivity. This example demonstrated Et_3N rather than the substitution pattern of arenes played a key factor for the catalytic *para*-C—H arylation reaction. However, *meta*-substituted substrates provided lower yields of arylated products than their *ortho*-substituted counterparts (**5.4i** vs **5.4a**, and **5.4j** vs **5.4d**). This trend might derive from the steric hindrance imparted by the *meta*-substituent to the *para*-position that disfavors the attack of α,α-difluoroketone enolates, thus reducing the yields and selectivity towards arylated products.

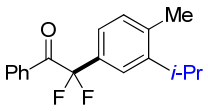
Table 5.4. Selective *para*-C–H Difluoroalkylation of Substrates Bearing Distinct Benzyl Moieties[a]



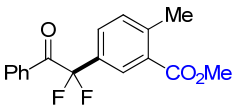
5.3a–j **5.4a–j**



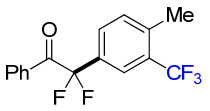
5.4a, 81% (72%)[b]



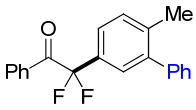
5.4b, 83% (77%)



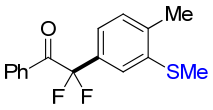
5.4c, 68% (65%)[c]
Ar:Bn = 11:1[d]



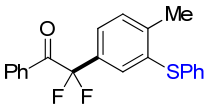
5.4d, 91% (83%)[e]



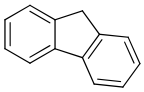
5.4e, 61% (52%)[f]



5.4f, 65% (60%)[g]

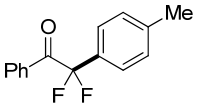


5.4g, 57% (52%)[h]
Ar:Bn = 10:1[d]

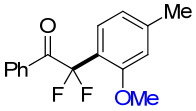


9*H*-fluorene, 35%

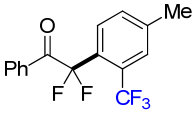
major side product for reaction of substrate **5.3e**



5.4h, 62% (57%)[j]



5.4i, 56% (52%)[j]

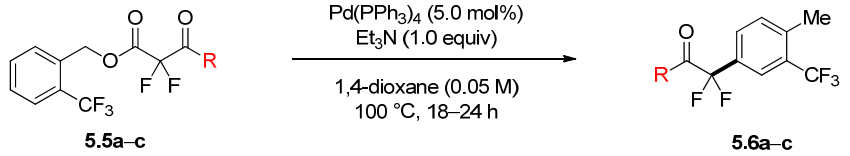


5.4j, 28% (27%)[j]
Ar:Bn = 8:1[d]

[a] Standard reaction conditions: **5.3a–j** (1.0 equiv), $Pd(PPh_3)_4$ (2.5 mol%), Et_3N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. ^{19}F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs). [b] 110 °C. [c] $Pd(PPh_3)_4$ (5.0 mol%), 120 °C, 12 h. [d] The ratio of arylated to benzylated products was determined by ^{19}F NMR analysis. [e] $Pd(PPh_3)_4$ (5.0 mol%), 18 h. [f] $Pd(PPh_3)_4$ (5.0 mol%), 24 h. [g] $Pd(PPh_3)_4$ (5.0 mol%), 120 °C, 24 h. [h] $Pd(PPh_3)_4$ (5.0 mol%), 1,4-dioxane (0.1 M), 120 °C, 24 h. [i] 24 h. [j] $Pd(PPh_3)_4$ (5.0 mol%), 24 h.

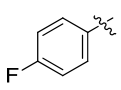
The decarboxylative arylation reaction also converted substrates bearing a variety of aryl, heteroaryl, and alkyl α,α-difluoroketones into the products (Table 5.5). The substrate bearing an electron-neutral aryl α,α-difluoroketone moiety (**5.5a**) provided the arylated product (**5.6a**) in high yields. Even, heteroaryl-containing α,α-difluoroketone substrate (**5.5b**) worked well under the standard reaction conditions. The tolerance to *S*- and *N*-containing heterocycles represented potential application of the current reaction toward accessing fluorinated analogues of biologically active molecules. Additionally, the reaction of an aliphatic α,α-difluoroketone substrate (**5.5c**) afforded good yield of the arylated product (**5.6c**) without further optimization.

Table 5.5. Selective *para*-C–H Difluoroalkylation of Substrates Bearing Distinct Ketone Moieties[a]

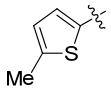


5.5a–c **5.6a–c**

R =



5.6a, 83% (79%)



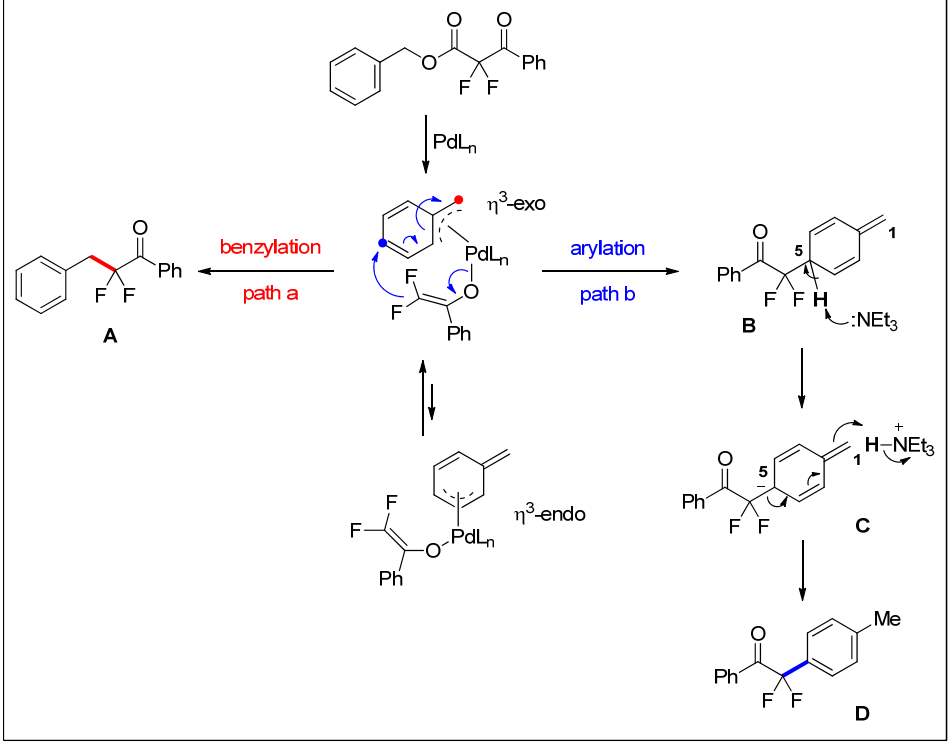
5.6b, 85% (80%)

5.6c, 80% (73%)

[a] Standard reaction conditions: **5.5a–c** (1.0 equiv), $Pd(PPh_3)_4$ (5.0 mol%), Et_3N (1.0 equiv),1,4-dioxane (0.05 M), 100 °C, 18–24 h. ^{19}F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs).

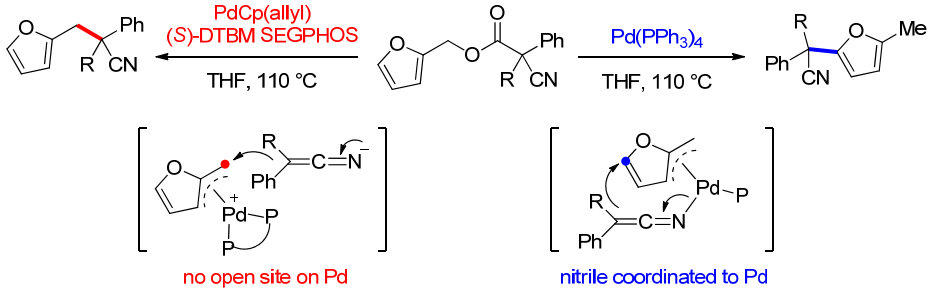
The α-aryl-α,α-difluoroketone products likely derive from a pathway that differs from that proposed for the formation of α-benzyl-α,α-difluoroketone products (Figure 5.1). In decarboxylative benzylation reactions, the α,α-difluoroketone enolate reacts with the benzylic position of (η^3-exobenzyl)palladium(II) intermediate by a S_N2-like reductive elimination, and forms the key C(α)–C(sp^3) bond (**A**, path a).[13] However, in the present decarboxylative C–H arylation reaction, the α,α-difluoroketone enolate might attack the *para*-position of the aromatic ring to form a dearomatized product (**B**, path b), which could undergo Et_3N-facilitated rearomatization to generate the α-aryl-α,α-difluoroketone products (**B**→**D**, path b).

Figure 5.1. Proposed Mechanism for the Formation of Arylated Products



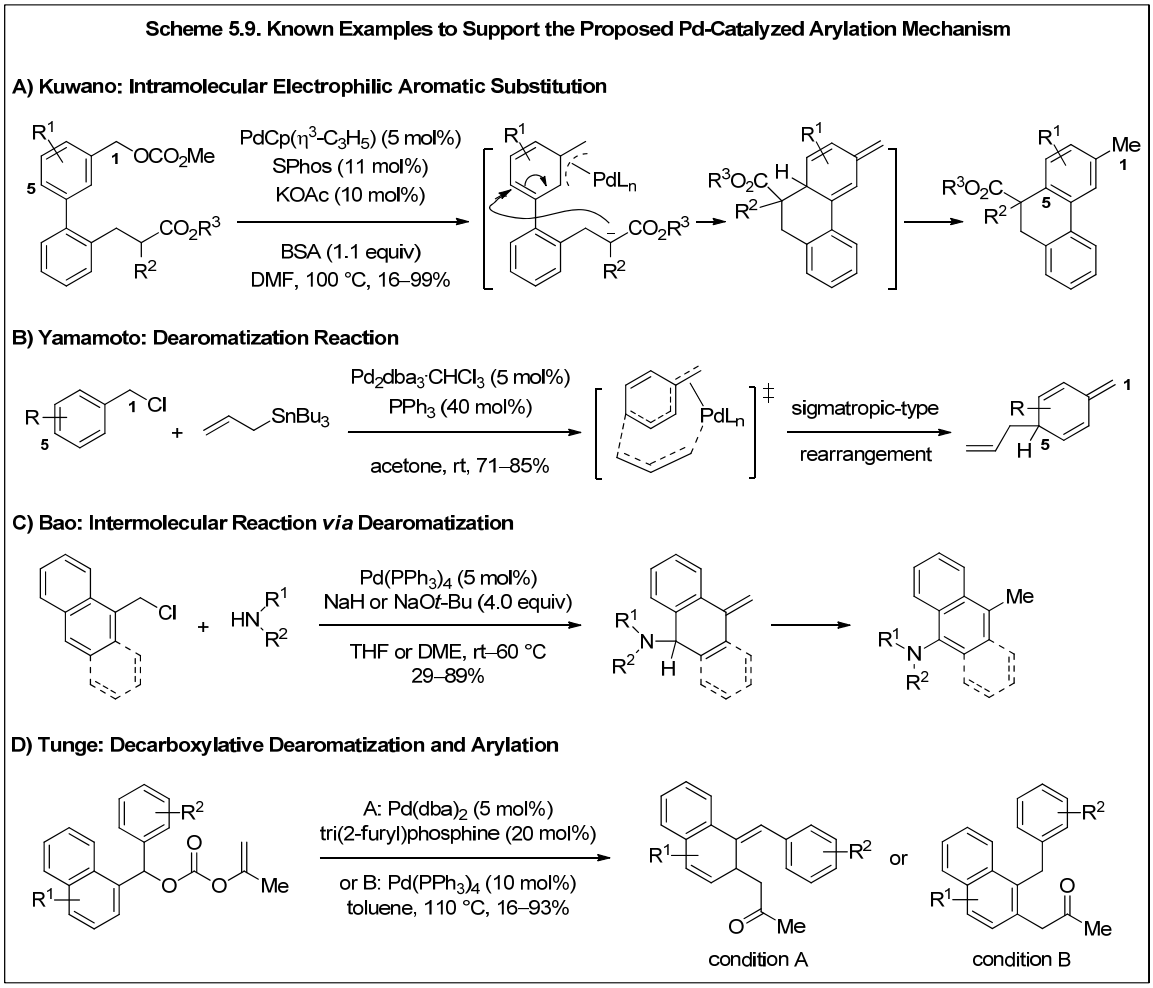
Such regioselective benzylation and arylation reactions have been reported by the Tunge lab (Figure 5.2).[14] In the reactions, the use of the bidentate (*S*)-DTBM SEGPHOS ligand provided benzylated products, while the utilization of the monodentate PPh_3 ligand generated arylated products. Thus, the selectivity between benzylation and arylation is controlled by the ligands. However, in our cases, Et_3N seems to play an important role in switching the selectivity from benzylation to arylation.

Figure 5.2. Ligands Controlled the Selectivity between Benzylation and Arylation



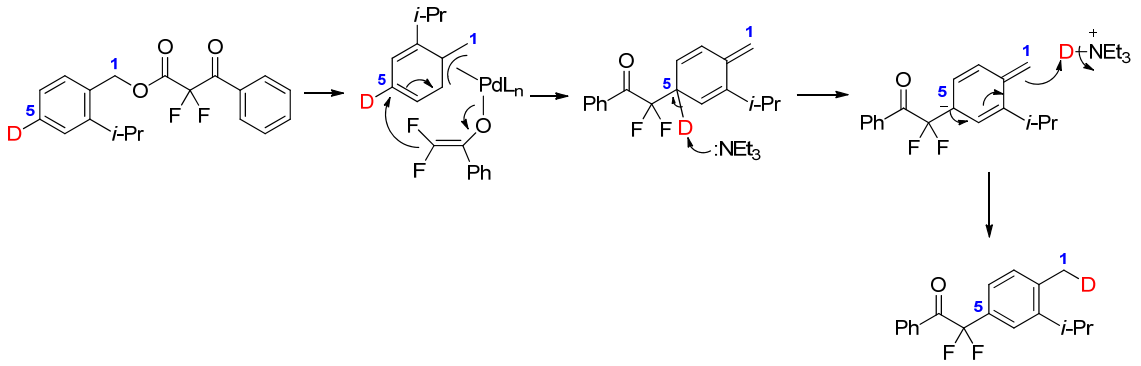
In support of the proposed arylation mechanism, the Kuwano lab illustrated benzylic carbonates bearing an internal nucleophile undergo the palladium-catalyzed cyclization reactions with the nucleophile attacking the *para*-position to form a dearomatized product that rearomatizes to the final product (Scheme 5.9A).[15 a] Moreover, the Yamamoto and Bao labs have reported intermolecular palladium-catalyzed dearomatization reactions, in which the nucleophiles, including allyltributylstannane and secondary amines, attack the aromatic *para*-position instead of the benzylic position to generate dearomatized and C–N coupling products (Scheme 5.9B and 5.9C).[15b,c] Additionally, the Tunge lab demonstrated decarboxylative coupling reactions of benzyl enol carbonates that can provide dearomatized and arylated ketone products using different palladium catalysts (Scheme 5.9D).[15d]

Scheme 5.9. Known Examples to Support the Proposed Pd-Catalyzed Arylation Mechanism



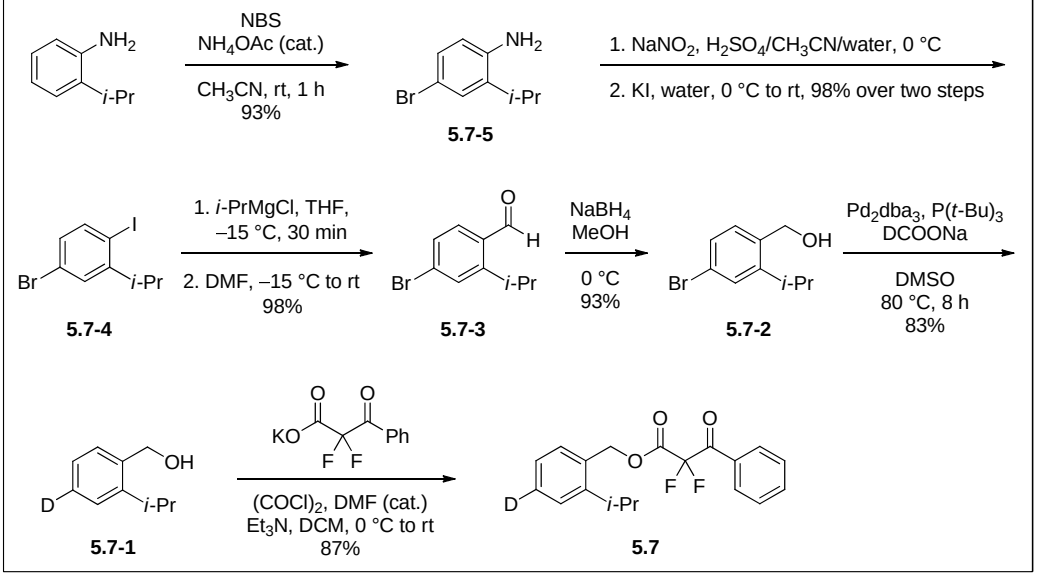
The proposed arylation mechanism involves a dearomatization-rearomatization process, in which a proton shifts from the C5 (*para*-position) to the C1 (benzylic position) position. To confirm the involvement of a 1,5-prototropic shift in our arylation reaction, we prepared a deuterium-labeled substrate with deuterium incorporated on the C5 position to observe if the deuterium could relocate to the C1 position (Scheme 5.10).

Scheme 5.10. A 1,5-Deuteron Transfer in the Proposed Mechanism to Access Arylated Products



The synthesis of the deuterium-labeled substrate **5.7** started with the commercially available 2-isopropylaniline, which underwent bromination followed by one-pot two-step nitration and iodination to generate aryl iodide **5.7-4**. Subsequent formylation of aryl iodide **5.7-4** and reduction of the aldehyde **5.7-3** formed benzyl alcohol **5.7-2**, which coupled with deuterated sodium formate to produce deuterated alcohol **5.7-1**.[16] Finally, the esterification of deuterated alcohol **5.7-1** with α,α-difluoro-β-keto acetate provided the deuterium-labeled probe **5.7** (95% of deuterium content) in good yields (Scheme 5.11).

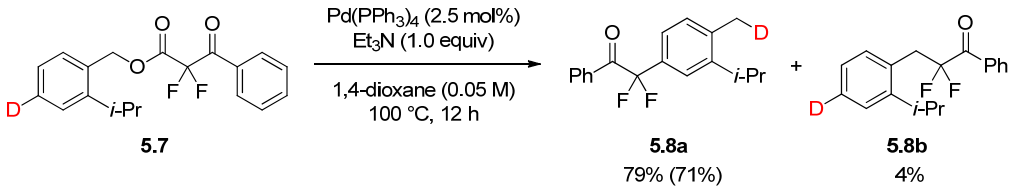
Scheme 5.11. Synthetic Sequence of Deuterium-Labeled Probe



5.7-5 **5.7-4** **5.7-3** **5.7-2** **5.7-1** **5.7**

To test the proposed 1,5-deuteron shift, the deuterium-labeled substrate **5.7** was subjected to the standard catalytic conditions (Scheme 5.12). This reaction generated the product **5.7a** with deuterium relocated to the C1 (benzylic position) in the yield (71%) comparable to the non-deuterium-labeled counterpart **5.4b** (77%). The result was consistent with the proposed mechanism. The dearomatization-rearomatization process occurs during the reactions and Et_3N might serve as a proton shuttle to facilitate such a process.

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

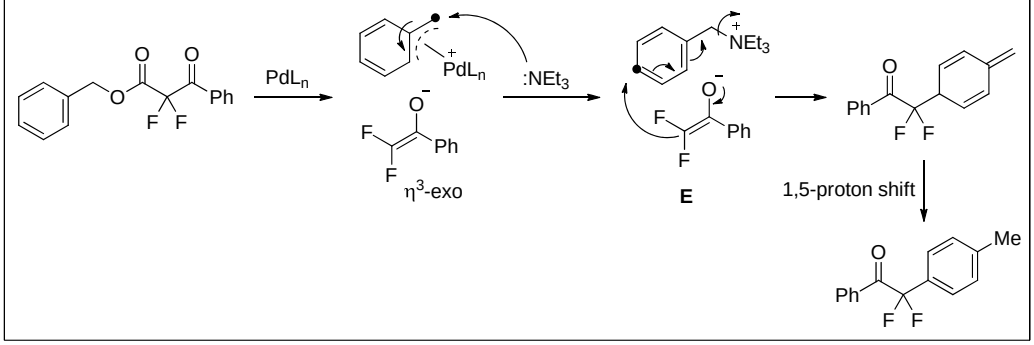


5.7 **5.8a** 79% (71%) **5.8b** 4%

[a] Standard reaction conditions: **5.7** (1.0 equiv), $Pd(PPh_3)_4$ (2.5 mol%), Et_3N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. ^{19}F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs).

Meanwhile, we still cannot exclude out the role of Et_3N as a nucleophile. For this, another mechanism is also considered for selective *para*-fluoroalkylation reaction of arenes (Scheme 5.13). In this mechanism, Et_3N might serve as a nucleophile to attack the benzylic position of (η^3-exobenzyl)palladium(II) intermediate and generate an activated benzylic electrophile **E**. Then, the benzylic electrophile **E** reacts with the α,α-difluoroketone enolate to form a dearomatized product, which rearomatizes to provide the arylated product.

Scheme 5.13. Another Possible Mechanism with Et_3N Serving as a Nucleophile



More studies to explain the role of Et_3N are necessary. Currently, mechanistic studies aiming to understand the origin for the selective *para*-C–H difluoroalkylation of arenes are in progress. This part of work is performed by Dr. Francisco de Azambuja in the lab. The proposed studies include 1) kinetic isotope effect (KIE) to understand if the cleavage of *para*-C–H bond is the rate-determining step; 2) the use of stoichiometric amount of deuterated methanol as an additive to see if the reaction involves the insertion of Pd catalyst into the C–H bond; 3) cross-over experiments to probe if the α,α-difluoroketone enolate dissociates from the (π-benzyl)palladium(II) complex; 4) competitive experiments of deuterated and non-deuterated substrates to probe the slowest step: oxidative addition or reductive elimination, and the role of Et_3N in the reaction; and 5) NMR experiments to elucidate if new intermediates form under the catalytic conditions. These results will be reported in the future.

5.3 Conclusion

Remote *para*-C–H functionalization of arenes has been a challenging topic. Current methods for *para*-selective activation of C–H bonds mainly rely on electronic control of substrates, and utilization of auxiliary groups, which causes limited substrate scope, and contradicts atom economy, respectively. In contrast, the ability to use simple additives to direct a catalytic reaction to a remote position provides a new and complementary opportunity for C–H functionalization reactions. We reported a palladium-catalyzed decarboxylative C–H difluoroalkylation reaction of arenes, in which Et_3N overrides the anticipated coupling pathway, and instead provides a C–H functionalization product with *para*-selectivity. This base-enabled C–H transformation tolerates electron-rich and -deficient substrates, and should provide an alternative strategy for designing *para*-selective functionalization reactions.

[1] (a) White, M. C. "Adding Aliphatic C–H Bond Oxidations to Synthesis" *Science* **2012**, *335*, 807–809. (b) Yoshikai, N.; Wei, Y. "Synthesis of Pyrroles, Indoles, and Carbazoles through Transition-Metal-Catalyzed C–H Functionalization" *Asian J. Org. Chem*. **2013**, *2*, 466–478. (c) Liu, B.; Hu, F.; Shi, B.-F. "Recent Advances on Ester Synthesis *via* Transition-Metal Catalyzed C–H Functionalization" *ACS Catal*. **2015**, *5*, 1863–1881. (d) Hartwig, J. F. "Evolution of C–H Bond Functionalization from Methane to Methodology" *J. Am. Chem. Soc*. **2016**, *138*, 2–24. (e) Hartwig, J. F.; Larsen, M. A. "Undirected, Homogeneous C–H Bond Functionalization: Challenges and Opportunities" *ACS Cent. Sci.* **2016**, *2*, 281–292. (f) Cui, Y.-M.; Lin, Y.; Xu, L.-W. "Catalytic Synthesis of Chiral Organoheteroatom Compounds of Silicon, Phosphorus, and Sulfur *via* Asymmetric Transition Metal-Catalyzed C–H Functionalization" *Coord. Chem. Rev*. **2017**, *330*, 37–52.

[2] (a) Labinger, J. A.; Bercaw, J. E. "Understanding and Exploiting C–H Bond Activation" *Nature* **2002**, *417*, 507–514. (b) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. "Designing Catalysts for Functionalization of Unactivated C–H Bonds Based on the CH Activation Reaction" *Acc. Chem. Res*. **2012**, *45*, 885–898. (c) Engle, K. M.; Yu, J.-Q. "Developing Ligands for Palladium(II)-Catalyzed C–H Functionalization: Intimate Dialogue between Ligand and Substrate" *J. Org. Chem*. **2013**, *78*, 8927–8955. (d) Landaeta, V. R.; Rodríguez-Lugo, R. E. "Insights on the C–H Bond Activation by Transition Metal Complexes from Groups 8-10 Bearing (P-N) Chelates" *J. Mol. Catal. A: Chem*. **2017**, *426*, 316–325. (e) Wencel-Delord, J.; Dröege, T.; Liu, F.; Glorius, F. "Towards Mild Metal-Catalyzed C–H Bond Activation" *Chem. Soc. Rev*. **2011**, *40*, 4740–4761.

[3] (a) Wencel-Delord, J.; Glorius, F. "C–H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules" *Nat. Chem*. **2013**, *5*, 369–375. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. "Recent Developments in Natural Product Synthesis Using Metal-Catalysed C–H Bond Functionalisation" *Chem. Soc. Rev*. **2011**, *40*, 1885–1898. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. "C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals" *Angew. Chem. Int. Ed*. **2012**, *51*, 8960–9009. (d) Rousseaux, S.; Liégault, B.; Fagnou, K. C–H Functionalization: A New Strategy for the Synthesis of Biologically Active Natural Products. In *Modern Tools for the Synthesis of Complex Bioactive Molecules*; Cossy, J.; Arseniyadis, S., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, **2012**; Chapter 1.

[4] (a) Godula, K.; Sames, D. "C–H Bond Functionalization in Complex Organic Synthesis" *Science* **2006**, *132*, 67–72. (b) Park, J.-W.; Jun, C.-H. "Transition Metal-Catalyzed Regioselective Functionalization of Aromatic Compounds" *ChemCatChem* **2009**, *1*, 69–71.

[5] (a) Ackermann, L.; Vicente, R. "Ruthenium-Catalyzed Direct Arylations through C–H Bond Cleavages" *Top. Curr. Chem*. **2010**, *292*, 211–229. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. "Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions" *Acc. Chem. Res*. **2012**, *45*, 788–802. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. "Rhodium Catalyzed Chelation-Assisted C–H Bond Functionalization Reactions" *Acc. Chem. Res*. **2012**, *45*, 814–825. (d) Zhang, F.; Spring, D. R. "Arene C—H Functionalisation Using a Removable/Modifiable or a Traceless Directing Group Strategy" *Chem. Soc. Rev*. **2014**, *43*, 6906–6919. (e) Song, G.; Li, X. "Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes" *Acc. Chem. Res*. **2015**, *48*, 1007–1020.

[6] (a) Zhou, Y.; Zhao, J.; Liu, L. "Meta-Selective Transition-Metal Catalyzed Arene C–H Bond Functionalization" *Angew. Chem. Int. Ed*. **2009**, *48*, 7126–7128. (b) Yang, J. "Transition Metal Catalyzed *meta*-C–H Functionalization of Aromatic Compounds" *Org. Biomol. Chem*. **2015**, *13*, 1930–1941. (c) Liu, L.; Wang, Q.; Zhu, R.; Huang, J. "A Masse Shot: Transition-Metal-Catalyzed Selective *meta*-C–H Functionalization (*ortho*-Metallation and *para*-Bromination Relay)" *Synlett* **2016**, *27*, 1450–1455. (d) Dey, A.; Agasti, S.; Maiti, D. "Palladium Catalysed *meta*-C–H Functionalization Reactions" *Org. Biomol. Chem*. **2016**, *14*, 5440–5453. (e) Zhang, Z.; Tanaka, K.; Yu, J.-Q. "Remote Site-Selective C–H Activation Directed by a Catalytic Bifunctional Template" *Nature* **2017**, *543*, 538–542.

[7] (a) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. "A Highly *Para*-Selective Copper(II)-Catalyzed Direct Arylation of Aniline and Phenol Derivatives" *Angew. Chem. Int. Ed*. **2011**, *50*, 458–462. (b) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. "Gold-Catalyzed Direct Arylation" *Science* **2012**, *337*, 1644–1648. (c) Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. "Regioselective Gold-Catalyzed Oxidative C–N Bond Formation" *Org. Lett*. **2015**, *17*, 358–361. (d) Berzina, B.; Sokolovs, I.; Suna, E. "Copper-Catalyzed *para*-Selective C–H Amination of Electron-Rich Arenes" *ACS Catal*. **2015**, *5*, 7008–7014. (e) Sokolovs, I.; Suna, E. "*Para*-Selective Cu-Catalyzed C–H Aryloxylation of Electron-Rich Arenes and Heteroarenes" *J. Org. Chem*. **2016**, *81*, 371–379.

[8] (a) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. "Highly Site-Selective Direct C–H Bond Functionalization of Phenols with α-Aryl-α-diazoacetates and Diazooxindoles *via* Gold Catalysis" *J. Am. Chem. Soc*. **2014**, *136*, 6904–6907. (b) Ma, B.; Chu, Z.; Huang, B.; Liu, Z.; Liu, L.; Zhang, J. "Highly *para*-Selective C–H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters" *Angew. Chem. Int. Ed*. **2017**, *56*, 2749–2753.

[9] (a) Wang, X.; Leow, D.; Yu, J.-Q. "Pd(II)-Catalyzed *para*-Selective C–H Arylation of Monosubstituted Arenes" *J. Am. Chem. Soc*. **2011**, *133*, 13864–13867. (b) Xu, H.; Shang, M.; Dai, H.-X.; Yu, J.-Q. "Ligand-Controlled *Para*-Selective C–H Arylation of Monosubstituted Arenes" *Org. Lett*. **2015**, *17*, 3830–3833. (c) Yang, Z.; Qiu, F.-C.; Gao, J.; Li, Z.-W.; Guan, B.-T. "Palladium-Catalyzed Oxidative Arylation of Tertiary Benzamides: *Para*-Selectivity of Monosubstituted Arenes" *Org. Lett*. **2015**, *17*, 4316–4319. (d) Wu, Z.; Luo, F.; Chen, S.; Li, Z.; Xiang, H.; Zhou, X. "Palladium-Catalyzed *para*-Selective Arylation of Phenols with Aryl Iodides in Water" *Chem. Commun*. **2013**, *49*, 7653–7655.

[10] (a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Bera, M.; Maiti, D. "Remote *para*-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly" *J. Am. Chem. Soc*. **2015**, *137*, 11888–11891. (b) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. "Palladium-Catalyzed Directed *para* C–H Functionalization of Phenols" *Angew. Chem. Int. Ed*. **2016**, *55*, 7751–7755.

[11] (a) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. "Bimetallic Nickel Aluminum Mediated *Para*-Selective Alkenylation of Pyridine: Direct Observation of η^2,η^1-Pyridine Ni(0) -Al(III) Intermediates Prior to C–H Bond Activation" *J. Am. Chem. Soc*. **2010**, *132*, 11887–11889. (b) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. "Selective C-4 Alkylation of Pyridine by Nickel /Lewis Acid Catalysis" *J. Am. Chem. Soc*. **2010**, *132*, 13666–13668. (c) Lee, W.-C.; Chen, C.-H.; Liu, C.-Y.; Yu, M.-S.; Lin, Y.-H.; Ong, T.-G. "Nickel-Catalyzed *para*-CH Activation of Pyridine with Switchable Regioselective Hydroheteroarylation of Allylarenes" *Chem. Commun*. **2015**, *51*, 17104–17107. (d) Okumura, S.; Tang, S.; Saito, T.; Semba, K.; Sakaki, S.; Nakao, Y. "*para*-Selective Alkylation of Benzamides and Aromatic Ketones by Cooperative Nickel/Aluminum Catalysis" *J. Am. Chem. Soc*. **2016**, *138*, 14699–14704. (e) Saito, Y.; Segawa, Y.; Itami, K. "*para*-C–H Borylation of Benzene Derivatives by a Bulky Iridium Catalyst" *J. Am. Chem. Soc*. **2015**, *137*, 5193–5198.

[12] Yang, M.-H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. "Palladium Catalysis Enables Benzylation of α,α-Difluoroketone Enolates" *Angew. Chem., Int. Ed*. **2016**, *55*, 9080–9083.

[13] (a) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. "Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions" *Chem. Rev*. **2011**, *111*, 1846–1913. (b) Trost, B. M.; Czabaniuk, L. C. "Structure and Reactivity of Late Transition Metal η^3-Benzyl Complexes" *Angew. Chem. Int. Ed.* **2014**, *53*, 2826–2851.

[14] Recio III, A.; Heinzman, J. D.; Tunge, J. A. "Decarboxylative Benzylation and Arylation of Nitriles" *Chem. Commun*. **2012**, *48*, 142–144.

[15] (a) Ueno, S.; Komiya, S.; Tanaka, T.; Kuwano, R. "Intramolecular S_N'-Type Aromatic Substitution of Benzylic Carbonates at their *Para*-Position" *Org. Lett*. **2012**, *14*, 338–341. (b) Bao, M.; Nakamura, H.; Yamamoto, Y. "Facile Allylative Dearomatization Catalyzed by Palladium" *J. Am. Chem. Soc*. **2001**, *123*, 759–760. (c) Zhang, S.; Wang, Y.; Feng, X.; Bao, M. "Palladium-Catalyzed Amination of Chloromethylnaphthalene and Chloromethylanthracene Derivatives with Various Amines" *J. Am. Chem.*

Soc. **2012**, *134*, 5492–5495. (d) Mendis, S. N.; Tunge, J. A. “Decarboxylative Dearomatization and mono-α-Arylation of Ketones” *Chem. Commun*. **2016**, *52*, 7695–7698.
[16] Zhang, H.-H.; Bonnesen, P. V.; Hong, K. “Palladium-Catalyzed Br/D Exchange of Arenes: Selective Deuterium Incorporation with Versatile Functional Group Tolerance and High Efficiency” *Org. Chem. Front*. **2015**, *2*, 1071–1075.

Chapter 5 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 5

Table of Contents

General Information

Unless otherwise noted, reactions were performed under an atmosphere of N_2 using oven-dried glassware. Palladium-catalyzed reactions were performed in 1 dram vials and 20 mL pressure-resistant scintillation vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with $KMnO_4$, anisaldehyde, phosphomolybdic acid or iodine. Column chromatography was conducted using an automated and manual system for purifying substrates and catalytic products, respectively. In most cases, arylated and benzylated products are very close to each other or on the same spot on TLC plate. To visualize their separation, the staining reagent phosphomolybdic acid can be used to distinguish arylated and benzylated products while they represent different color. ^{19}F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. 1,4-Dioxane (anhydrous), $Pd(PPh_3)_4$ (reagent grade, 99%), and Et_3N (anhydrous) were purchased from Sigma Aldrich. Solvents including DMF, PhMe, CH_2Cl_2, THF, MeOH were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual $CHCl_3$ in the NMR solvent ($CHCl_3$: $\delta = 7.27$ ppm or DMSO-d_6: $\delta = 2.50$ ppm).

Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak ($CDCl_3$: δ = 77.23 ppm or DMSO-d_6: δ = 39.51 ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ^{19}F NMR chemical shifts (δ) are reported in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pent, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer or by atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Infrared spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

Preparation of Known Compounds

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

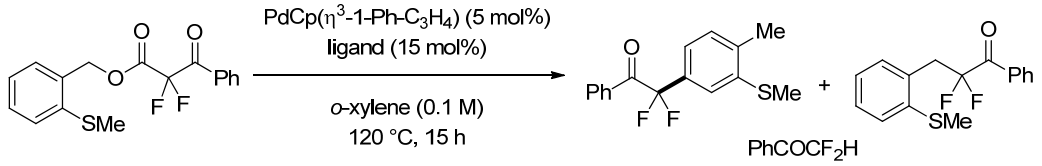
General Procedure for Screening Conditions

An oven-dried 1 dram vial was charged with substrate **5.1** (0.100 mmol), Pd catalysts, ligands (for ligand screening), bases (for base screening), a magnetic stir bar, and anhydrous solvents inside the glove box. Subsequently, the vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The

sealed vial was placed on a pre-heated reaction block at the indicated temperature with stirring for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.5 mL). α,α,α-Trifluorotoluene (10 μL, 0.0814 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis.

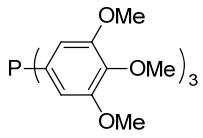
Initial Screening and Optimization of Reaction Conditions

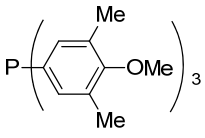
Table 1. Electron-Rich Triphenylphosphine Ligands Favored Formation of Arylated Product

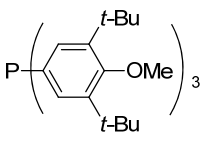


entry	ligand	arylation (%)	benzylation (%)	$PhCOCF_2H$ (%)	conv. (%)
1	$P(4\text{-}CF_3C_6H_4)_3$	4	1	2	15
2	PPh_3	33	2	22	88
3	$PPh_2(4\text{-}OMeC_6H_4)$	35	2	27	93
4	$PPh(4\text{-}OMeC_6H_4)_2$	32	2	29	92
5	$P(4\text{-}OMeC_6H_4)_3$	30	1	32	93
6	$P(4\text{-}NMe_2C_6H_4)_3$	0	0	17	37

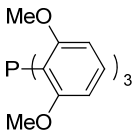
Other ligands screened that produced < 25% arylated product by ^{19}F NMR analysis were shown below.

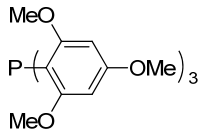


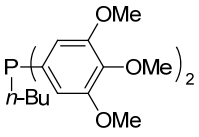




Xantphos
DPEPhos
t-BuXantphos
rac-BINAP
dppBz
dppe
dppp
dppf



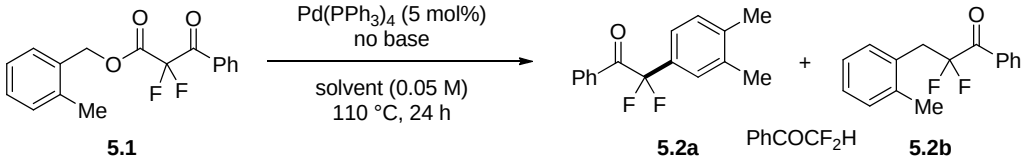




PCy_3
$P(t\text{-}Bu)_3$
tri(2-furyl)phosphine
$P(4\text{-}MeC_6H_4)_3$
$P(4\text{-}PhC_6H_4)_3$
$P(2\text{-}OMeC_6H_4)_3$

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

Table 2. Solvents Affected Selectivity between Benzylation and Arylation[a,b]

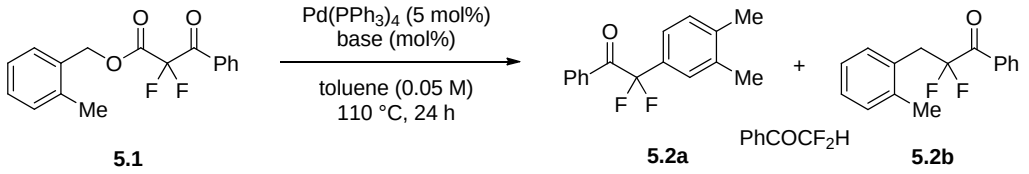


5.1 **5.2a** $PhCOCF_2H$ **5.2b**

entry	solvent	**5.2a** (%)	**5.2b** (%)	$PhCOCF_2H$ (%)
1	o-xylene	0	97	2
2	1,4-dioxane	0	quant.	0
3	anisole	0	quant.	0
4	diglyme	2	87	4
5	butyronitrile	42	7	25
6	DMA	45	8	25
7	DMF	47	8	27
8	DMSO	24	6	50

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.
[b] Full conversion was observed except for entry 4 (conv. 97%)

Table 3. Bases Remarkably Affected Selectivity between Benzylation and Arylation[a,b]



5.1 **5.2a** **5.2b**

entry	base (mol%)	**5.2a** (%)	**5.2b** (%)	$PhCOCF_2H$ (%)
1	-	0	89	0
2	butyronitrile (300)	0	88	3
3	Na_2CO_3 (300)	0	91	3
4	PhONa (100)	0	0	18
5	$PhCO_2K$ (100)	2	71	6
6	pyridine (100)	4	85	0
7	*N*, *N*-dimethylaniline (100)	0	89	2
8	DMAP (100)	54	4	17
9	N(*n*-Pr)$_3$ (100)	58	13	6
10	Et_3N (100)	70	5	6
11	TMEDA (100)	69	5	8
12	quinuclidine (100)	12	1	10
13	DIPEA (100)	12	68	4
14	Et_3N (50)	65	7	5
15	Et_3N (25)	63	11	5
16	Et_3N (10)	49	26	4
17	Et_3N (300)	69	5	5
18[c]	Et_3N (100)	82 (75)	7	6

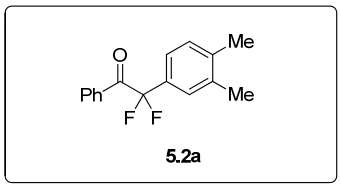
[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.
[b] Full conversion was observed.
[c] The optimized conditions: **5.1** (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), Et_3N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. ^{19}F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs)

Experimental Procedures for Pd-Catalyzed Arylation of α,α-Difluoroketone Enolates

General Procedure A: An oven-dried 20 mL scintillation vial was charged with substrate **5.1**, **5.3a–j** (0.500 mmol), Et_3N (70 μL, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry 1,4-dioxane (0.010 L) was added *via* a syringe. Subsequently, the vial was sealed, transferred out of the glove box and placed on a pre-heated reaction block at 100 °C, and stirred for 12 h. The vial was

cooled to rt, and the mixture was diluted with EtOAc (1 mL). α,α,α-Trifluorotoluene (30 μL, 0.2443 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 15 mins to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis. After determining the ^{19}F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of celite, and eluted with EtOAc. Removal of the solvents under reduced pressure and chromatographic purification provided the desired product **5.2a** and **5.4a**–**j**.

Experimental Procedures and Characterization of Compounds for Table 5.3



5.2a

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

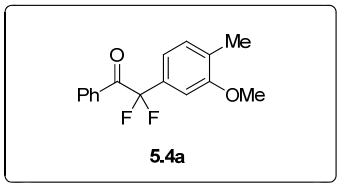
General procedure A was followed using **5.1** (152 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.2a** as an off-white solid (100 mg, 77%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04–8.01 (m, 2 H), 7.61–7.56 (m, 1 H), 7.47–7.42 (m, 2 H), 7.37 (s, 1 H), 7.37–7.35 (m, 1 H), 7.22 (d, J = 8.0 Hz, 1 H), 2.29 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.4 (t, J = 31.2 Hz), 140.1, 137.6, 134.3, 132.4, 130.7 (t, J = 25.2 Hz), 130.5 (t, J = 2.7 Hz), 130.3, 128.8, 126.8 (t, J = 5.8 Hz), 123.1 (t, J = 5.9 Hz), 117.2 (t, J = 252.6 Hz), 20.1, 19.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 3061, 2924, 1701, 1597, 1580, 1504, 1449, 1300, 1261, 1175, 1126, 918, 851, 826, 723, 685, 644, 517 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2ONa$ $[M+Na]^+$ 283.0910, found 283.0921. mp 47–48 °C.

Experimental Procedures and Characterization of Compounds for Table 5.4

General Procedure B: An oven-dried one-neck round-bottom flask was charged with aldehyde (14 mmol). Methanol (30 mL) was added as solvent, followed by the addition of $NaBH_4$ (21 mmol) as solid portion. The reaction mixture was stirred at 0 °C for 30 min. H_2O was added to quench the reaction, and methanol

was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) three times and the combined organic phases were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 30%) for elution to afford the desired benzyl alcohol.

General Procedure C: An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate (7.2 mmol), and the system was evacuated and backfilled with $N_{2(g)}$ three times. Dry CH_2Cl_2 (35 mL) and DMF (0.19 mL) were added *via* a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (6.9 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. Next, a solution of benzyl alcohol derivative (6.0 mmol) dissolved in dry CH_2Cl_2 (3.0 mL) was added dropwise at 0 °C, followed by dropwise addition of Et_3N (12 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. H_2O (10 mL) was added to quench the reaction, and the CH_2Cl_2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 25 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

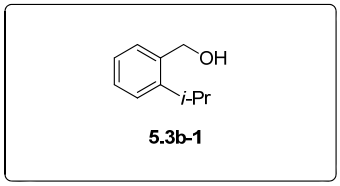


5.4a

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

General procedure A was followed using **5.3a** (160 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 110 °C. Workup and chromatographic purification (10% to 25% DCM in hexanes) provided the title compound **5.4a** as an off-white solid (100 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (dt, *J* = 7.4, 1.1 Hz, 2 H), 7.59 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 7.03 (s, 1 H), 3.85 (s, 3 H), 2.24 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.3 (t, *J* = 30.6 Hz), 158.2, 134.3, 132.4, 131.9 (t, *J* = 25 Hz), 131.1, 130.5 (t, *J* = 2.5 Hz), 130.3, 128.8, 117.6 (t, *J* =6.2 Hz), 117.1 (t, *J* = 251.2

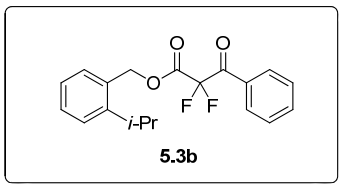
Hz), 106.9 (t, J = 5.6 Hz), 55.6, 16.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 2959, 2938, 1699, 1597, 1508, 1450, 1410, 1294, 1265, 1223, 1175, 1128, 1047, 918, 849, 822, 712, 687, 656 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2O_2$ $[M]^+$ 276.0962, found 276.0952. mp 51–52 °C.



5.3b-1

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

General procedure B was followed using 2-isopropylbenzaldehyde[2] (1.97 g, 13.3 mmol), $NaBH_4$ (0.760 g, 20.0 mmol), and MeOH (28 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **5.3b-1** as a colorless oil (1.68 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.29 (m, 3 H), 7.20 (td, J = 7.1, 1.7 Hz, 1 H), 4.77 (d, J = 5.6 Hz, 2 H), 3.28 (hept, J = 6.8 Hz, 1 H), 1.51 (t, J = 6.0 Hz, 1 H), 1.27 (d, J = 6.8 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.4, 137.5, 128.6, 128.5, 126.1, 125.7, 63.5, 28.8, 24.2. IR (film) 3342, 2962, 2928, 2870, 1489, 1450, 1385, 1184, 1034, 1005, 758 cm^{-1}.

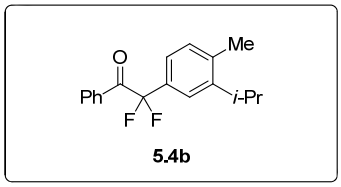


5.3b

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (1.4 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), **5.3b-1** (0.75 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), DMF (0.15 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3b** as a colorless oil (1.35 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (dd, J = 8.8, 1.2 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.49 (dd, J = 8.4, 7.4 Hz, 2 H), 7.38–7.28 (m, 3 H), 7.17 (ddd, J = 7.5, 6.7, 1.9 Hz, 1 H), 5.41 (s, 2 H), 3.09 (hept, J = 6.8 Hz, 1 H), 1.20 (d, J = 6.8 Hz, 12 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 148.6, 135.3, 131.1 (t, J = 1.9 Hz),

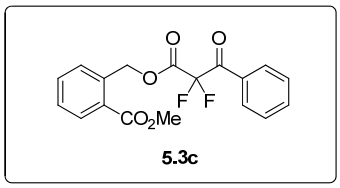
130.7, 130.4, 130.1 (t, J = 1.9 Hz), 130.0, 129.1, 126.1, 126.0, 110.0 (t, J = 263.7 Hz), 67.6, 29.2, 24.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3067, 2966, 1774, 1715, 1699, 1599, 1493, 1450, 1385, 1308, 1257, 1157, 1101, 922, 802, 760, 712, 685 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{18}F_2O_3K$ $[M+K]^+$ 371.0861, found 371.0862.



5.4b

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

General procedure A was followed using **5.3b** (166 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.4b** as a colorless oil (112 mg, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (dt, J = 8.3, 1.2 Hz, 2 H), 7.60–7.57 (m, 1 H), 7.48 (d, J = 2.0 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.32 (dd, J = 8.0, 2.0 Hz, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 3.16 (hept, J = 6.9 Hz, 1 H), 2.37 (s, 3 H), 1.22 (d, J = 6.9 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.5 (t, J = 31.2 Hz), 147.9, 138.6, 134.3, 132.5, 131.1 (t, J = 25.0 Hz), 130.8, 130.5 (t, J = 2.9 Hz), 128.8, 122.9 (t, J = 5.9 Hz), 122.2 (t, J = 5.8 Hz), 117.4 (t, J = 252.7 Hz), 29.6, 23.2, 19.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 3063, 2965, 1703, 1597, 1499, 1449, 1252, 1221, 1182, 1132, 920, 885, 826, 714, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{18}F_2ONa$ $[M+Na]^+$ 311.1223, found 311.1216.

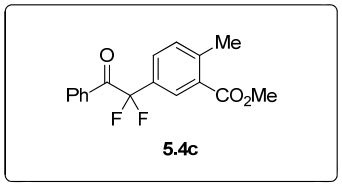


5.3c

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (1.9 g, 7.9 mmol), oxalyl chloride (0.64 mL, 7.6 mmol), methyl 2-(hydroxymethyl)benzoate[3] (1.1 g, 6.6 mmol), Et_3N (1.8 mL, 13 mmol), DMF (0.20 mL), and CH_2Cl_2 (40 mL). Workup and chromatographic purification (5%

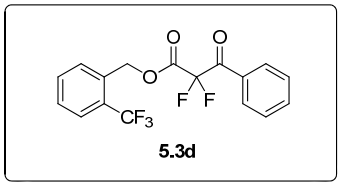
to 10% EtOAc in hexanes) afforded the title compound **5.3c** as a colorless oil (1.4 g, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dt, *J* = 7.4, 1.0 Hz, 2 H), 8.02 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.70–7.66 (m, 1 H), 7.54–7.49 (m, 3 H), 7.44–7.39 (m, 2 H), 5.78 (s, 2 H), 3.88 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.5 (t, *J* = 27.5 Hz), 167.0, 161.7 (t, *J* = 30.6 Hz), 135.8, 135.3, 132.9, 131.3, 131.2, 130.2 (t, *J* = 2.5 Hz), 129.2, 128.6 (overlap), 128.5, 110.1 (t, *J* = 263.1 Hz), 67.6, 52.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.7 (s, 2 F). IR (film) 3071, 2955, 1778, 1714, 1697, 1599, 1582, 1493, 1450, 1435, 1383, 1306, 1269, 1128, 1082, 959, 924, 791, 741, 712, 687, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{14}F_2O_5Na$ $[M+Na]^+$ 371.0707, found 371.0703.



5.4c

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

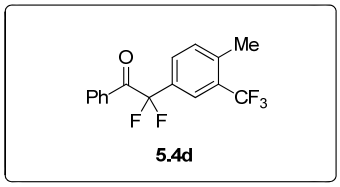
General procedure A was followed using **5.3c** (174 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 120 °C. Workup and chromatographic purification (15% to 50% DCM in hexanes) provided the title compound **5.4c** as a colorless oil (100 mg, 66%; a 11:1 mixture of the arylated to benzylated isomers by ^{19}F NMR analysis). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, *J* = 2.0 Hz, 1 H), 8.06–8.03 (m, 2 H), 7.64–7.59 (m, 2 H), 7.49–7.45 (m, 2 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 3.91 (s, 3 H), 2.65 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.9 (t, *J* = 31.2 Hz), 167.2, 143.7, 134.6, 132.6, 132.1, 131.0 (t, *J* = 25.0 Hz), 130.5 (t, *J* = 3.1 Hz), 130.3, 129.1 (t, *J* = 5.6 Hz), 128.9, 128.2 (t, *J* = 5.6 Hz), 116.8 (t, *J* = 252.5 Hz), 52.3, 21.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.9 (s, 2 F). IR (film) 3073, 2953, 1732, 1703, 1597, 1449, 1310, 1267, 1229, 1132, 1084, 970, 907, 835, 779, 721, 687, 644 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3Na$ $[M+Na]^+$ 327.0809, found 327.0821.



5.3d

2-(trifluoromethyl)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3d)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (0.86 g, 3.6 mmol), oxalyl chloride (0.29 mL, 3.4 mmol), 2-trifluoromethylbenzyl alcohol (0.53 g, 3.0 mmol), Et_3N (0.83 mL, 6.0 mmol), DMF (93 μL), and CH_2Cl_2 (18 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3d** as a colorless oil (0.70 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09–8.06 (m, 2 H), 7.71–7.66 (m, 2 H), 7.58–7.45 (m, 5 H), 5.54 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.7 (t, *J* = 30.6 Hz), 135.4, 132.5, 132.1, 131.0 (t, *J* = 1.9 Hz), 130.3, 130.1 (t, *J* = 2.5 Hz), 129.2, 129.1, 128.6 (q, *J* = 30.9 Hz), 126.4 (q, *J* = 5.4 Hz), 124.1 (q, *J* = 272.1 Hz), 110.1 (t, *J* = 263.7 Hz), 65.4 (q, *J* = 2.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.7 (s, 2 F), –60.4 (s, 3 F). IR (film) 3075, 1780, 1701, 1599, 1450, 1315, 1167, 1121, 1061, 924, 770, 712, 685, 654, 581 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{11}F_5O_3Na$ $[M+Na]^+$ 381.0526, found 381.0536.

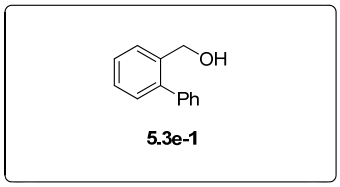


5.4d

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

General procedure A was followed using **5.3d** (179 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.4d** as a colorless oil (131 mg, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08–8.06 (m, 2 H), 7.87 (d, *J* = 1.9 Hz, 1 H), 7.66–7.62 (m, 2 H), 7.51–7.48 (m, 2 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 2.54 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.7 (t, *J* = 31.5 Hz), 140.2 (m), 134.7, 132.7, 132.0, 131.3 (t, *J* = 25.8 Hz), 130.5 (t, *J* = 2.8 Hz), 129.8 (q, *J* = 30.7 Hz), 129.2 (t, *J* = 5.8 Hz), 129.0, 124.1 (q, *J* = 272.5 Hz), 123.5 (h, *J* = 5.8 Hz), 116.8 (t,

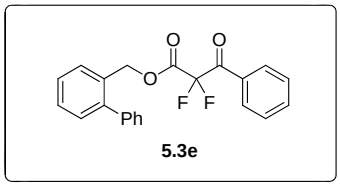
J = 254.4 Hz), 19.5 (m). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.8 (s, 2 F), –62.5 (s, 3 F). IR (film) 3075, 2940, 1705, 1624, 1597, 1504, 1450, 1327, 1236, 1211, 1175, 1130, 1059, 1026, 905, 833, 806, 716, 687, 673, 613 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_5O$ $[M+H]^+$ 315.0808, found 315.0800.



5.3e-1

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

Compound **5.3e-1** was prepared from a known procedure[4] using 2-phenylbenzoic acid (2.0 g, 10 mmol), LAH (0.76 g, 20 mmol), and THF (50 mL) under refluxing. Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound **5.3e-1** as an off-white solid (1.37 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (dd, J = 7.2, 2.0 Hz, 1 H), 7.46–7.35 (m, 7 H), 7.30 (dd, J = 7.0, 1.8 Hz, 1 H), 4.64 (d, J = 6.0 Hz, 2 H), 1.57 (t, J = 5.8 Hz, 1 H). Spectroscopic data matched that from the previous report.[5] mp 43–44 °C (lit. 44 °C).[6]

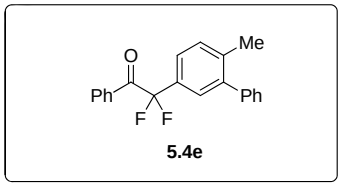


5.3e

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (1.3 g, 5.4 mmol), oxalyl chloride (0.44 mL, 5.2 mmol), **5.3e-1** (0.83 g, 4.5 mmol), Et_3N (1.2 mL, 9.0 mmol), DMF (0.14 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3e** as a colorless oil (1.45 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 8.4, 1.6 Hz, 2 H), 7.71–7.66 (m, 1 H), 7.51 (t, J = 7.8 Hz, 2 H), 7.46–7.26 (m, 9 H), 5.26 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, J = 26.9 Hz), 161.7 (t, J = 30.6 Hz), 143.0, 140.0, 135.3, 131.2 (overlap), 130.4, 130.2, 130.1 (t, J = 2.5 Hz), 129.3, 129.2 (overlap), 128.5, 127.9, 127.7, 110.0 (t, J = 263.7 Hz), 67.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3063, 3028, 1771, 1715, 1699,

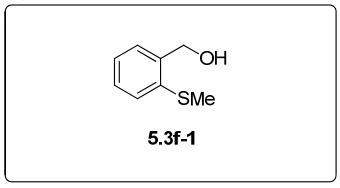
1599, 1481, 1450, 1381, 1312, 1099, 1011, 922, 802, 746, 704, 685, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{22}H_{16}F_2O_3Na$ $[M+Na]^+$ 389.0965, found 389.0979.



5.4e

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

General procedure A was followed using **5.3e** (183 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (5% to 25% DCM in hexanes) provided the title compound **5.4e** as a colorless oil (86 mg, 53%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09–8.07 (m, 2 H), 7.63–7.59 (m, 1 H), 7.54–7.37 (m, 8 H), 7.34–7.31 (m, 2 H), 2.33 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (t, *J* = 31.2 Hz), 142.7, 140.9, 138.9 (t, *J* = 2.5 Hz), 134.4, 132.4, 131.1, 130.9 (t, *J* = 25 Hz), 130.5 (t, *J* = 2.5 Hz), 129.3, 128.8, 128.4, 127.5, 127.1 (t, *J* = 5.6 Hz), 124.6 (t, *J* = 6.2 Hz), 117.2 (t, *J* = 251.2 Hz), 20.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 3059, 3028, 1703, 1597, 1489, 1449, 1267, 1227, 1128, 1105, 899, 827, 770, 702, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{17}F_2O$ $[M+H]^+$ 323.1247, found 323.1244.

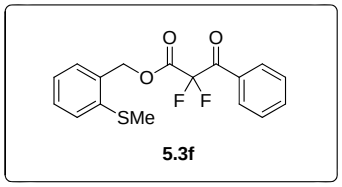


5.3f-1

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

Compound **5.3f-1** was prepared from a known procedure[4] using 2-(methylthio)benzoic acid (1.3 g, 8.0 mmol), LAH (0.61 g, 16 mmol), and THF (40 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound **5.3f-1** as a colorless oil (1.1 g, 89%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J* = 7.6 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.22–7.18 (m, 1 H), 4.77 (s, 2 H), 2.50 (s, 3 H),

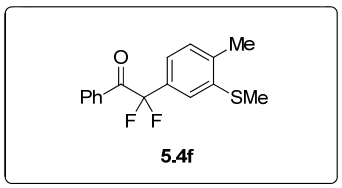
2.13 (br, 1 H). Spectroscopic data matched that from the previous report.[4] HRMS (ESI, *m/z*): calcd for C_8H_9OS $[M-H]^+$ 153.0374, found 153.0369.



5.3f

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (1.8 g, 7.8 mmol), oxalyl chloride (0.63 mL, 7.5 mmol), **5.3f-1** (1.0 g, 6.5 mmol), Et_3N (1.8 mL, 13 mmol), DMF (0.20 mL), and CH_2Cl_2 (38 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3f** as a colorless oil (1.74 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dt, *J* = 7.6, 1.1 Hz, 2 H), 7.66 (tt, *J* = 7.6, 1.4 Hz, 1 H), 7.52–7.47 (m, 2 H), 7.35–7.28 (m, 3 H), 7.18–7.14 (m, 1 H), 5.46 (s, 2 H), 2.43 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.3 (t, *J* = 26.9 Hz), 161.8 (t, *J* = 30.6 Hz), 138.7, 135.2, 132.2, 131.2, 130.1 (t, *J* = 2.5 Hz), 129.8 (overlap), 129.1, 127.5, 125.7, 109.9 (t, *J* = 263.1 Hz), 67.4, 16.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3065, 2924, 1778, 1770, 1713, 1697, 1597, 1472, 1450, 1381, 1310, 1256, 1157, 1101, 1080, 922, 800, 750, 712, 685, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_3SNa$ $[M+Na]^+$ 359.0529, found 359.0542.

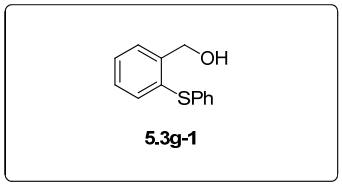


5.4f

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

General procedure A was followed using **5.3f** (168 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.4f** as an off-white solid (90 mg, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 8.1 Hz, 2 H), 7.62–7.58 (m, 1 H), 7.47–7.44 (m, 2 H), 7.34 (d, *J* = 1.8 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 2.48

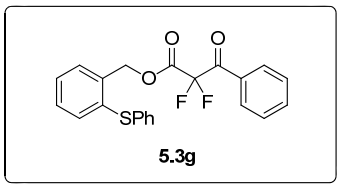
(s, 3 H), 2.35 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.2 (t, *J* = 31.1 Hz), 139.5, 138.7, 134.3, 132.3, 131.6 (t, *J* = 25.0 Hz), 130.5 (t, *J* = 2.8 Hz), 130.2, 128.9, 121.7 (t, *J* = 6.0 Hz), 121.0 (t, *J* = 6.0 Hz), 117.1 (t, *J* = 253.3 Hz), 20.1, 15.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.8 (s, 2 F). IR (film) 3063, 2922, 1703, 1597, 1449, 1393, 1267, 1242, 1130, 1105, 1036, 908, 824, 721, 685, 644 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{15}F_2OS$ $[M+H]^+$ 293.0812, found 293.0801. mp 46–47 °C.



5.3g-1

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

Compound **5.3g-1** was prepared from a known procedure[4] using 2-(phenylthio)benzoic acid[7] (3.0 g, 13 mmol), LAH (1.0 g, 27 mmol), and THF (65 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound **5.3g-1** as an off-white solid (2.5 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54–7.51 (m, 1 H), 7.40–7.34 (m, 2 H), 7.31–7.26 (m, 3 H), 7.24–7.19 (m, 3 H), 4.79 (d, *J* = 6.4 Hz, 2 H), 2.06 (t, *J* = 6.4 Hz, 1 H). Spectroscopic data matched that from the previous report.[8] HRMS (ESI, *m/z*): calcd for $C_{13}H_{12}OS$ $[M]^+$ 216.0609, found 216.0602. mp 43–44 °C (lit. 44 °C).

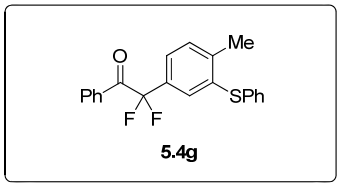


5.3g

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (0.95 g, 4.0 mmol), oxalyl chloride (0.32 mL, 3.8 mmol), **5.3g-1** (0.71 g, 3.3 mmol), Et_3N (0.92 mL, 6.6 mmol), DMF (0.10 mL), and CH_2Cl_2 (20 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3g** as a colorless oil (0.93 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 7.6 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.41–7.17 (m, 9 H), 5.51 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.3 (t, *J* = 27.5 Hz), 161.7 (t, *J* = 30.6 Hz), 135.7, 135.4, 135.3, 134.7, 134.0,

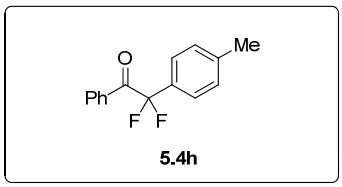
131.2, 130.2, 130.1, 129.9, 129.7, 129.5, 129.1, 128.4, 127.1, 110.0 (t, J = 263.7 Hz), 67.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3063, 1776, 1713, 1697, 1597, 1581, 1477, 1450, 1441, 1377, 1308, 1256, 1157, 1099, 1024, 924, 800, 746, 712, 687, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{22}H_{16}F_2O_3SNa$ $[M+Na]^+$ 421.0686, found 421.0688.



5.4g

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

General procedure A was followed using **5.3g** (199 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (5.0 mL). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.4g** as a colorless oil (103 mg, 58%; a 10:1 mixture of the arylated to benzylated isomers by ^{19}F NMR analysis). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–7.95 (m, 2 H), 7.62–7.57 (m, 1 H), 7.45–7.39 (m, 4 H), 7.33–7.26 (m, 4 H), 7.24–7.21 (m, 2 H), 2.41 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.8 (t, J = 31.2 Hz), 142.3, 136.2, 134.5, 134.4, 132.1, 131.8 (t, J = 25.0 Hz), 131.1, 130.9, 130.4 (t, J = 2.5 Hz), 129.6, 128.8 (overlap), 127.4, 124.7 (t, J = 5.6 Hz), 116.8 (t, J = 252.5 Hz), 20.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –98.0 (s, 2 F). IR (film) 3061, 2922, 1713, 1699, 1597, 1582, 1476, 1449, 1387, 1242, 1130, 1024, 908, 824, 721, 687 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{17}F_2OS$ $[M+H]^+$ 355.0968, found 355.0954.

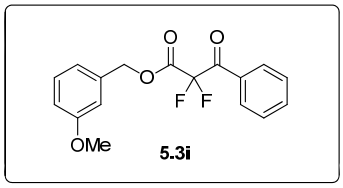


5.4h

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

General procedure A was followed using **5.3h** (145 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 10% DCM in hexanes) provided the title compound **5.4h** as a

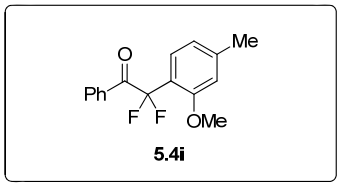
colorless oil (72 mg, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04–8.02 (m, 2 H), 7.61–7.57 (m, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.47–7.42 (m, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 2.39 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 189.3 (t, *J* = 30.9 Hz), 141.4, 134.3, 132.4, 130.5 (t, *J* = 2.9 Hz), 129.7, 128.8, 125.7 (t, *J* = 6.0 Hz), 117.3 (t, *J* = 252.6 Hz), 21.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.7 (s, 2 F). IR (film) 3063, 2926, 1699, 1597, 1448, 1259, 1186, 1122, 1095, 1007, 897, 822, 781, 725, 687, 627, 586, 542 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{13}F_2O$ $[M+H]^+$ 247.0934, found 247.0927.



5.3i

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

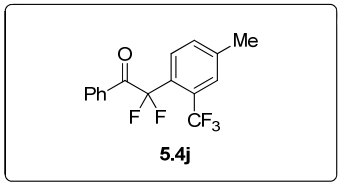
General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (2.0 g, 8.4 mmol), oxalyl chloride (0.69 mL, 8.1 mmol), 3-methoxybenzyl alcohol (0.97 g, 7.0 mmol), Et_3N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH_2Cl_2 (42 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.3i** as a colorless oil (1.6 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06–8.03 (m, 2 H), 7.69–7.65 (m, 1 H), 7.52–7.47 (m, 2 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 6.90–6.86 (m, 2 H), 6.85–6.84 (m, 1 H), 5.32 (s, 2 H), 3.79 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 159.9, 135.4, 135.3, 131.1 (t, *J* = 1.9 Hz), 130.1 (t, *J* = 2.5 Hz), 130.0, 129.2, 120.7, 114.8, 113.8, 110.0 (t, *J* = 263.7 Hz), 69.1, 55.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.9 (s, 2 F). IR (film) 2963, 2839, 1778, 1715, 1697, 1599, 1489, 1454, 1379, 1310, 1267, 1126, 916, 783, 685, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{14}F_2O_4Na$ $[M+Na]^+$ 343.0758, found 343.0766.



5.4i

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

General procedure A was followed using **5.3i** (160 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (2% to 4% EtOAc in hexanes) provided the title compound **5.4i** as an off-white solid (73 mg, 53%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97–7.94 (m, 2 H), 7.68 (d, *J* = 7.6 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.42–7.38 (m, 2 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 6.67 (s, 1 H), 3.58 (s, 3 H), 2.38 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 188.6 (t, *J* = 30.0 Hz), 156.7 (t, *J* = 5.3 Hz), 143.3, 133.6, 133.1, 129.7 (t, *J* = 2.2 Hz), 128.5, 126.3 (t, *J* = 6.8 Hz), 121.9, 120.6 (t, *J* = 24.1 Hz), 115.4 (t, *J* = 250.3 Hz), 112.8, 55.6, 22.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.9 (s, 2 F). IR (film) 2939, 1716, 1614, 1585, 1508, 1464, 1414, 1284, 1238, 1167, 1148, 1121, 1038, 1005, 928, 901, 862, 816, 717, 690, 646, 604 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{14}F_2O_2Na$ $[M+Na]^+$ 299.0860, found 299.0858. mp 53–54 °C.



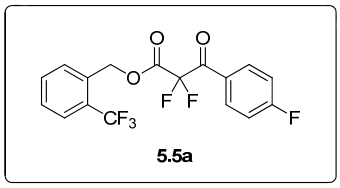
5.4j

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

General procedure A was followed using **5.3j** (179 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 10% DCM in hexanes) provided the title compound **5.4j** as a colorless oil (40 mg, 25%; a 11:1 mixture of the arylated to benzylated isomers by ^{19}F NMR analysis). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17–8.14 (m, 2 H), 7.70–7.64 (m, 2 H), 7.63 (s, 1 H), 7.55–7.51 (m, 2 H), 7.49 (d, *J* = 7.2 Hz, 1 H), 2.49 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 188.8 (t, *J* = 33.0 Hz), 141.7, 134.4, 132.5, 132.2 (t, *J* = 3.0 Hz), 130.4 (t, *J* = 2.5 Hz), 128.9, 128.5 (q, *J* = 5.4 Hz), 128.3 (t, *J* = 9.8 Hz), 123.7 (q, *J* = 272.0 Hz), 117.6 (t, *J* = 256.9 Hz), 21.4. (Two set of peaks buried between 128.6 and 128.2 ppm). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –94.1 (q, *J* = 11.3 Hz, 2 F), –58.6 (t, *J* = 11.3 Hz, 3 F) for the arylated isomer; δ –99.0 (t, *J* = 17.6 Hz, 2 F), –63.2 (s, 3 F) for the benzylated isomer. IR (film) 3072,

2928, 1701, 1599, 1450, 1315, 1277, 1240, 1136, 1074, 893, 854, 820, 717, 692, 650 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{12}F_5O$ $[M+H]^+$ 315.0808, found 315.0787.

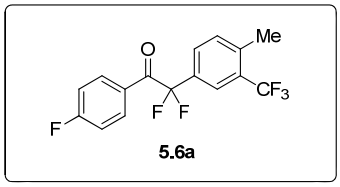
Experimental Procedures and Characterization of Compounds for Table 5.5



5.5a

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

General procedure C was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate[1] (1.1 g, 4.2 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), 2-trifluoromethylbenzyl alcohol (0.62 g, 3.5 mmol), Et_3N (0.97 mL, 7.0 mmol), DMF (0.11 mL), and CH_2Cl_2 (21 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) or (15% to 30% DCM in hexanes) afforded the title compound **5.5a** as a colorless oil (0.76 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (ddt, *J* = 7.5, 5.3, 1.1 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.60–7.52 (m, 2 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.21–7.16 (m, 2 H), 5.54 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.0 (t, *J* = 27.5 Hz), 167.1 (d, *J* = 258.7 Hz), 161.5 (t, *J* = 30.6 Hz), 133.2 (dt, *J* = 9.6, 3.1 Hz), 132.5, 132.0, 130.5, 129.2, 128.7 (q, *J* = 30.8 Hz), 127.5 (q, *J* = 2.5 Hz), 126.5 (q, *J* = 5.4 Hz), 124.1 (q, *J* = 272.1 Hz), 116.6 (d, *J* = 22.5 Hz), 110.1 (t, *J* = 263.7 Hz), 65.5 (q, *J* = 2.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.6 (s, 2 F), –100.7 (m, 1 F), –60.4 (s, 3 F). IR (film) 3082, 1778, 1697, 1599, 1510, 1456, 1416, 1315, 1244, 1123, 1040, 926, 851, 768, 654, 613, 571 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{11}F_6O_3$ $[M+H]^+$ 377.0612, found 377.0606.

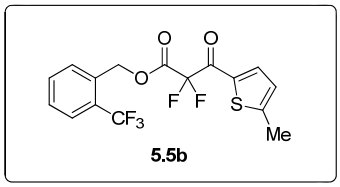


5.6a

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

General procedure A was followed using **5.5a** (188 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup

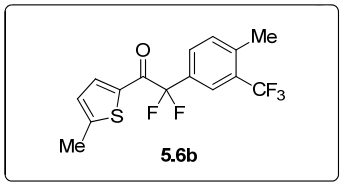
and chromatographic purification (5% to 10% DCM in hexanes) provided the title compound **5.6a** as a colorless oil (132 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14–8.10 (m, 2 H), 7.84 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.20–7.14 (m, 2 H), 2.55 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.2 (t, *J* = 31.9 Hz), 166.7 (d, *J* = 256.2 Hz), 140.3 (m), 133.4 (dt, *J* = 10.0, 3.1 Hz), 132.7, 131.0 (t, *J* = 25.0 Hz), 129.8 (q, *J* = 30.4 Hz), 129.2 (t, *J* = 5.6 Hz), 128.4 (q, *J* = 2.5 Hz), 124.1 (q, *J* = 272.5 Hz), 123.5 (h, *J* = 5.7 Hz), 116.8 (t, *J* = 253.1 Hz), 116.4 (d, *J* = 22.5 Hz), 19.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –102.1 (m, 1 F), –97.6 (s, 2 F), –62.5 (s, 3 F). IR (film) 3084, 2941, 1705, 1601, 1508, 1414, 1327, 1285, 1238, 1175, 1130, 1059, 908, 853, 791, 766, 669, 604 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{11}F_6O$ $[M+H]^+$ 333.0714, found 333.0711.



5.5b

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

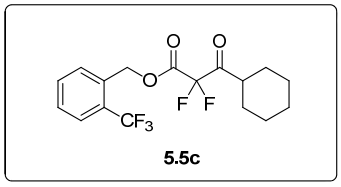
General procedure C was followed using potassium potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate[1] (1.5 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), 2-trifluoromethylbenzyl alcohol (0.88 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), DMF (0.15 mL), and CH_2Cl_2 (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound **5.5b** as a yellow oil (1.3 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.85 (m, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.59–7.52 (m, 2 H), 7.47 (t, *J* = 7.8 Hz, 1 H), 6.89 (dd, *J* = 4.0, 1.2 Hz, 1 H), 5.54 (s, 2 H), 2.59 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8 (t, *J* = 28.7 Hz), 161.5 (t, *J* = 31.2 Hz), 154.8, 137.5 (t, *J* = 5.0 Hz), 135.1, 132.5, 132.2, 130.1, 129.0, 128.5 (q, *J* = 31.2 Hz), 128.2, 126.4 (q, *J* = 5.8 Hz), 124.1 (q, *J* = 271.6 Hz), 109.8 (t, *J* = 263.7 Hz), 65.3 (q, *J* = 2.7 Hz), 16.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –108.2 (s, 2 F), –60.5 (s, 3 F). IR (film) 3078, 2926, 1778, 1682, 1666, 1447, 1315, 1171, 1124, 1040, 935, 812, 770, 675, 654, 582 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{11}F_5O_3SNa$ $[M+Na]^+$ 401.0247, found 401.0252.



5.6b

2,2-difluoro-2-(4-methyl-3-(trifluoromethyl)phenyl)-1-(5-methylthiophen-2-yl)ethanone (5.6b)

General procedure A was followed using **5.5b** (189 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.6b** as an off-white solid (134 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (s, 1 H), 7.84–7.83 (m, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 6.87 (dd, *J* = 4.0, 1.2 Hz, 1 H), 2.57 (s, 3 H), 2.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.4 (t, *J* = 31.9 Hz), 153.8, 140.1 (m), 137.1 (t, *J* = 5.0 Hz), 135.8, 132.6, 131.3 (t, *J* = 25.6 Hz), 129.7 (q, *J* = 30.4 Hz), 129.2 (t, *J* = 6.2 Hz), 128.0, 124.1 (q, *J* = 272.1 Hz), 123.5 (h, *J* = 6.0 Hz), 116.3 (t, *J* = 252.5 Hz), 19.5 (m), 16.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –99.4 (s, 2 F), –62.5 (s, 3 F). IR (film) 2928, 1672, 1624, 1445, 1327, 1285, 1238, 1211, 1175, 1126, 1059, 910, 860, 816, 773, 739, 683, 608 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{15}H_{12}F_5OS$ $[M+H]^+$ 335.0529, found 335.0520. mp 44–45 °C.

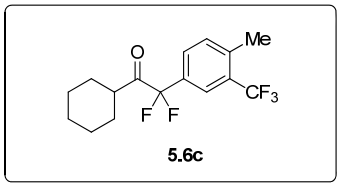


5.5c

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

General procedure C was followed using potassium potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate [1] (1.8 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 2-trifluoromethylbenzyl alcohol (1.1 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH_2Cl_2 (36 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) or (15% to 30% DCM in hexanes) afforded the title compound **5.5c** as a colorless oil (0.83 g, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 8.0 Hz, 1 H), 7.63–7.54 (m, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 2.93–2.86 (m, 1 H), 1.90–1.77 (m, 4 H), 1.72–1.67 (m,

1 H), 1.45–1.19 (m, 5 H), 5.51 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.2 (t, *J* = 26.9 Hz), 161.5 (t, *J* = 30.6 Hz), 132.5, 132.1, 130.5, 129.2, 128.8 (q, *J* = 30.8 Hz), 126.5 (q, *J* = 5.4 Hz), 124.1 (q, *J* = 272.5 Hz), 108.8 (t, *J* = 264.4 Hz), 65.3 (q, *J* = 2.9 Hz), 45.5, 28.2, 25.6, 25.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –113.2 (s, 2 F), –60.4 (s, 3 F). IR (film) 2938, 2860, 1782, 1738, 1611, 1587, 1452, 1315, 1175, 1123, 1061, 1040, 959, 770, 654 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{17}F_5O_3Na$ $[M+Na]^+$ 387.0996, found 387.1014.



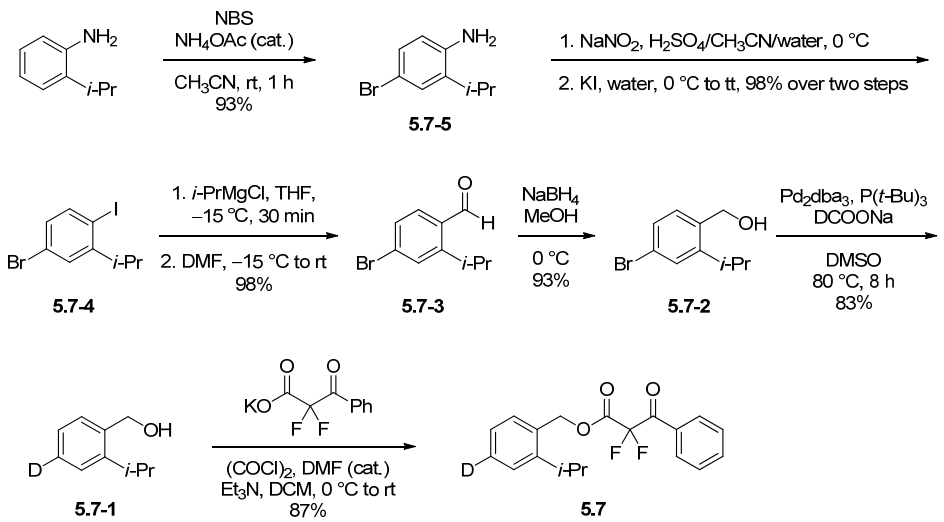
5.6c

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

General procedure A was followed using **5.5c** (182 mg, 0.500 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 1% DCM in hexanes) provided the title compound **5.6c** as a colorless oil (118 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (s, 1 H), 7.59 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 2.95–2.88 (m, 1 H), 2.54 (s, 3 H), 1.81–1.75 (m, 4 H), 1.71–1.67 (m, 1 H), 1.43–1.19 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8 (t, *J* = 30.6 Hz), 140.1, 132.6, 130.6 (t, *J* = 26.2 Hz), 129.7 (q, *J* = 30.4 Hz), 129.2 (t, *J* = 6.2 Hz), 124.1 (q, *J* = 272.5 Hz), 123.4 (h, *J* = 5.9 Hz), 115.7 (t, *J* = 253.7 Hz), 45.3, 28.8, 25.7, 25.5, 19.5 (m). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –105.6 (s, 2 F), –62.5 (s, 3 F). IR (film) 2938, 2860, 1738, 1624, 1452, 1327, 1287, 1240, 1175, 1128, 1059, 947, 908, 841, 829, 752, 681 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{16}H_{18}F_5O$ $[M+H]^+$ 321.1278, found 321.1267.

Preparation of Deuterium-Labeled Probe 5.7

Table 11. Synthetic Sequence of Deuterium-Labeled Probe



4-bromo-2-isopropylaniline (5.7-5)

Compound **5.7-5** was prepared from a previously reported procedure[9] using 2-isopropylaniline (8.5 mL, 60 mmol), NBS (12g, 66 mmol), NH4OAc (0.46 g, 6.0 mmol), and CH_3CN (0.24 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) provided the title compound **5.7-5** as a brown oil (12 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, *J* = 2.4 Hz, 1 H), 7.11 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 3.65 (br, 2 H), 2.85 (hept, *J* = 6.8 Hz, 1 H), 1.25 (d, *J* = 6.8 Hz, 6 H). Spectroscopic data matched that from the previous report.[9] HRMS (ESI, *m/z*): calcd for $C_9H_{13}BrN$ $[M+H]^+$ 214.0231, found 214.0239.

4-bromo-1-iodo-2-isopropylbenzene (5.7-4)

Compound **5.7-4** was prepared from a known procedure[10] using compound **5.7-5** (6.0 g, 28 mmol), H_2SO_4 (47 mL), CH_3CN (31 mL), $NaNO_2$ (3.5 g, 50 mmol), KI (16 g, 98 mmol), and water (0.12 L; 45 mL for dilution of H_2SO_4, 30 mL for solution of $NaNO_2$, and 45 mL for solution of KI). Workup followed by decolorization using $Na_2S_2O_3$ (sat'd), and chromatographic purification (hexanes) provided the title compound **5.7-4** as an orange oil (8.9 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 8.4 Hz, 1 H), 7.35 (d, *J* = 2.4 Hz, 1 H), 7.02 (dd, *J* = 8.0, 2.4 Hz, 1 H), 3.14 (hept, *J* = 6.8 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz,

6 H). Spectroscopic data matched that from the previous report.[9] HRMS (ESI, *m/z*): calcd for $C_9H_{10}BrI$ $[M]^+$ 323.9011, found 323.9007.

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

Compound **5.7-3** was prepared from a previously reported procedure using a slight modification.[11] Under an atmosphere of nitrogen, a solution of isopropylmagnesium chloride (2.0 M in THF, 57.5 mL, 115 mmol) was added dropwise to a solution of compound **5.7-4** (7.50 g, 23.0 mmol) in THF (80 mL) through an addition funnel at –15 °C. After stirring at –15 °C for 30 min, DMF (11.0 mL, 138 mmol) was added dropwise by an addition funnel, and then the mixture was stirred at –15 °C for another 2 h. Subsequently, the reaction mixture was gradually warmed to rt, and was continually stirred at rt for another 2 hr. Next, the resulting reaction mixture was added with 1N $HCl_{(aq)}$ at 0 °C until the solid formed in the reaction mixture dissolved. The two phases were transferred to a separation funnel, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 5%) for elution, and the product was dried by a rotatory evaporator (not high vacuum) to provide the compound **5.7-3** as a yellow oil (5.1 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.32 (s, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.59 (d, *J* = 1.6 Hz, 1 H), 7.50 (dd, *J* = 8.2, 1.8 Hz, 1 H), 3.95 (hept, *J* = 6.8 Hz, 1 H), 1.31 (d, *J* = 6.8 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.4, 153.4, 133.0, 131.9, 129.8 (overlap of three carbons), 27.9, 23.9. IR (film) 2967, 2870, 2731, 1703, 1694, 1584, 1557, 1464, 1389, 1288, 1213, 1150, 1097, 1059, 901, 835, 818, 758 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_{12}BrO$ $[M+H]^+$ 227.0072, found 227.0062.

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

General procedure B was followed using compound **5.7-3** (970 mg, 4.27 mmol), $NaBH_4$ (242 mg, 6.40 mmol), and MeOH (0.0120 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound **5.7-2** as an off-white solid (910 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 2.0 Hz, 1 H), 7.32 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 4.71 (d, *J* =

5.2 Hz, 2 H), 3.21 (hept, J = 6.8 Hz, 1 H), 1.56 (br, 1 H), 1.25 (d, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 136.4, 130.1, 129.1, 129.0, 122.5, 62.8, 28.9, 24.0. IR (film) 3395, 2963, 2870, 1589, 1566, 1485, 1462, 1398, 1223, 1101, 1040, 1003, 897, 880, 841, 814 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{10}H_{13}BrO$ $[M]^+$ 228.0150, found 228.0151. mp 64–65 °C.

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

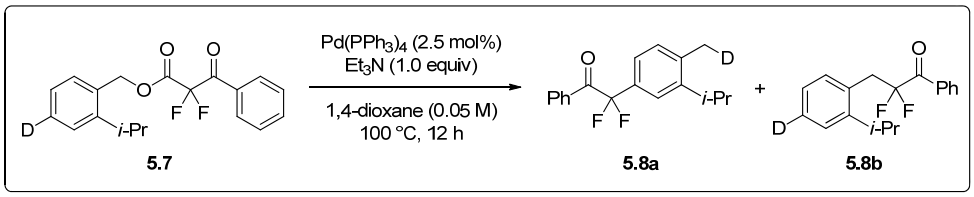
Compound **5.7-1** was prepared from a previously reported procedure using a slight modification.[12] An oven-dried microwave tube was charged with compound **5.7-2** (458 mg, 2.00 mmol), DCOONa (414 mg, 6.00 mmol), Pd_2dba_3 (36.6 mg, 0.0400 mmol), P(*t*-Bu)$_3$ (24.3 mg, 0.120 mmol), and dry DMSO (2.0 mL). Subsequently, the tube was sealed, and moved out of the glove box. The sealed tube was put into a pre-heated oil-bath at 80 °C, and stirred for 8 h. The tube was then removed out of the oil-bath, and cooled to rt. The reaction mixture was quenched with 2.0 mL of NH_4Cl (sat'd), and diluted with 6.0 mL of water. The mixture was transferred to a separation funnel, and the aqueous layer was extracted with DCM (4 x 12 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 5%) for elution to provide the compound **5.7-1** as a colorless oil (250 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 7.6 Hz, 1 H), 7.35 (s, 1 H), 7.20 (dd, J = 7.6, 1.6 Hz, 1 H), 4.77 (d, J = 4.8 Hz, 2 H), 3.28 (hept, J = 6.8 Hz, 1 H), 1.52 (t, J = 5.2 Hz, 1 H), 1.27 (d, J = 6.8 Hz, 6 H). ^{2}H NMR ($CHCl_3$, 61.4 MHz) δ 7.33 (s, 1 D). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.4, 137.4, 128.6, 128.3 (t, J = 24.4 Hz), 125.9, 125.6, 63.5, 28.8, 24.2. IR (film) 3331, 2963, 2928, 2870, 1599, 1483, 1462, 1410, 1182, 1026, 1007, 907, 851, 669, 523 cm^{-1}.

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

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate[1] (834 mg, 3.50 mmol), oxalyl chloride (0.28 mL, 3.36 mmol), compound **5.7-1** (442 mg, 2.92 mmol), Et_3N (0.81 mL, 5.84 mmol), DMF (91 μL), and CH_2Cl_2 (18 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound **5.7** as a colorless oil (848 mg, 87%). ^{1}H NMR ($CDCl_3$,

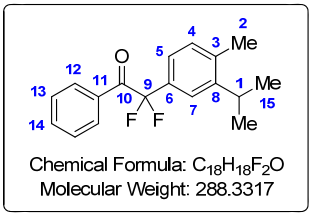
400 MHz) δ 8.04 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.33 (s, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 5.41 (s, 2 H), 3.09 (hept, *J* = 6.8 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 6 H). ^{2}H NMR ($CHCl_3$, 61.4 MHz) δ 7.36 (s, 1 D). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.4 (t, *J* = 27.5 Hz), 161.9 (t, *J* = 30.6 Hz), 148.6, 135.3, 131.1, 130.7, 130.4, 130.1 (t, *J* = 2.5 Hz), 129.7 (t, *J* = 24.4 Hz), 129.1, 126.0, 125.9, 110.0 (t, *J* = 263.1 Hz), 67.6, 29.2, 24.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3067, 2967, 1774, 1715, 1697, 1599, 1450, 1385, 1310, 1157, 1101, 1026, 922, 841, 799, 712, 675, 584 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{17}DF_2O_3Na$ $[M+Na]^+$ 356.1184, found 356.1190.

Procedures of Deuterium-Labeling Experiments in Scheme 5.12



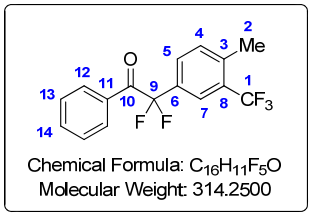
General procedure A was followed using **5.7** (167 mg, 0.500 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.0125 mmol), Et_3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 12 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound **5.8a** as a colorless oil (104 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04–8.02 (m, 2 H), 7.60–7.56 (m, 1 H), 7.48 (d, *J* = 1.2 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.33–7.30 (m, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 3.15 (hept, *J* = 6.8 Hz, 1 H), 2.35 (br, 2 H), 1.22 (d, *J* = 6.8 Hz, 6 H). ^{2}H NMR ($CHCl_3$, 61.4 MHz) δ 2.35 (t, *J* = 2.2 Hz,1 D). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.5 (t, *J* = 31.2 Hz), 147.9, 138.5, 134.2, 132.5, 131.1 (t, *J* = 25.0 Hz), 130.8, 130.5 (t, *J* = 2.5 Hz), 128.8, 122.9 (t, *J* = 5.6 Hz), 122.2 (t, *J* = 5.6 Hz), 117.4 (t, *J* = 251.2 Hz), 29.5, 23.2, 19.2 (m). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 2965, 2932, 1703, 1597, 1499, 1449, 1244, 1217, 1132, 924, 887, 824, 714, 679 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{18}DF_2O$ $[M+H]^+$ 290.1467, found 290.1459.

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



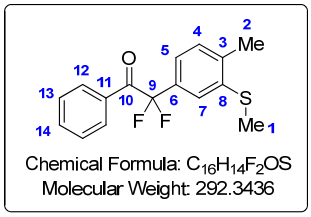
^{1}H (500 MHz), ^{13}C (125 MHz)	Solvent: $CDCl_3$	Notebook: MHY-11-221-Ar	Compound **5.4b**

Atom	**^{1}H shift (ppm)**	**Hs**	**Mult. (^{1}H)**	***J* (Hz)**	**^{13}C shift (ppm)**	**Type C**	**Mult. (^{13}C)**	***J* (Hz)**	**HMBC**	**COSY**	**NOESY**
1	3.16	1	hept	6.9	29.6	CH	s		4, 7, 15	15	2, 15
2	2.37	3	s		19.5	CH_3	s		4, 7	4	1, 4, 15
3					138.6	C	s		1, 2, 5, 7		
4	7.21	1	d	8.0	130.8	CH	s		2, 4	2, 5	2, 5
5	7.32	1	dd	8.0, 2.0	122.9	CH	t	5.9	7	4	4
6					131.1	C	t	25.0			
7	7.48	1	d	2.0	122.2	CH	t	5.8	1, 2, 5		15
8					147.9	C	s		1, 2, 4, 15		
9					117.4	C	t	252.7	5, 7		
10					189.5	C	t	31.2	12, 13		
11					132.5	C	s		13		
12	8.03	2	dt	8.3, 1.2	130.5	CH	t	2.9	12. 14	13	13
13	7.44	2	m	7.46–7.42	128.8	CH	s		13	12, 14	12, 14
14	7.58	1	m	7.60–7.57	134.3	CH	s		12	13	13
15	1.22	6	d	6.9	23.2	CH_3	s		1, 15	1	1, 2, 7



^{1}H (500 MHz), ^{13}C (125 MHz)	Solvent: $CDCl_3$	Notebook: MHY-11-219-Ar	Compound **5.4d**

Atom	**^{1}H shift (ppm)**	**Hs**	**Mult. (^{1}H)**	***J* (Hz)**	**^{13}C shift (ppm)**	**Type C**	**Mult. (^{13}C)**	***J* (Hz)**	**HMBC**	**COSY**	**NOESY**
1					124.1	CF_3	q	272.5			
2	2.54	3	s		19.5	CH_3	m		4, 7	4, 7	4
3					140.2	C	m		2, 5, 7		
4	7.41	1	d	8.0	132.7	CH	s		2	2	2, 5
5	7.65 (L)	1	m	7.66–7.62	129.2	CH	t	5.8	7	4	4
6					131.3	C	t	25.8	4		
7	7.87	1	d	1.9	123.5	CH	h	5.8	5	2	
8					129.8	C	q	30.7	2		
9					116.8	C	t	254.4	5, 7		
10					188.7	C	t	31.5	12		
11					132.0	C	s		13		
12	8.07	2	m	8.08–8.06	130.5	CH	t	2.8	12. 14	13	13
13	7.49	2	m	7.51–7.48	129.0	CH	s		13	12, 14	12, 14
14	7.63 (R)	1	m	7.66–7.62	134.7	CH	s		12	13	13



^{1}H (500 MHz), ^{13}C (125 MHz)	Solvent: $CDCl_3$	Notebook: MHY-11-273-Ar	Compound **5.4f**

Atom	**^{1}H shift (ppm)**	**Hs**	**Mult. (^{1}H)**	***J* (Hz)**	**^{13}C shift (ppm)**	**Type C**	**Mult. (^{13}C)**	***J* (Hz)**	**HMBC**	**COSY**	**NOESY**
1	2.48	3	s		15.2	CH_3	s		2	7	7
2	2.35	3	s		20.1	CH_3	s		1, 4	4	4
3					138.7	C	s		2, 5, 7		
4	7.22	1	d	8.0	130.2	CH	s		2	2, 5	2
5	7.29	1	d	8.0	121.7	CH	t	6.0	7	4	
6					131.6	C	t	25.0	4		
7	7.34	1	d	1.8	121.0	CH	t	6.0	5	1	1
8					139.5	C	s		1, 2, 4		
9					117.1	C	t	253.3	7		
10					189.2	C	t	31.1	12, 13		
11					132.3	C	s		13		
12	8.03	2	d	8.1	130.5	CH	t	2.8	12. 14	13	13
13	7.46	2	m	7.47–7.44	128.9	CH	s		13	12, 14	12, 14
14	7.60	1	m	7.62–7.58	134.3	CH	s		12	13	13

References for Chapter 5 Experimental Section

[1](a) Yang, M.-H.; Orsi, D. L.; Altman, R. A. "Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation Reaction to Access α,α-Difluoroketones" *Angew. Chem., Int. Ed*. **2015**, *54*, 2361–2365. (b) Yang, M.-H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. "Palladium Catalysis Enables Benzylation of α,α-Difluoroketone Enolates" *Angew. Chem., Int. Ed*. **2016**, *55*, 9080–9083.

[2] (a) The preparation of 2-isopropylbenzaldehyde was followed by the literature procedure. Casarini, D.; Lunazzi, L.; Mazzanti, A. "Correlated Rotations in Benzylfluorene Derivatives: Structure, Conformation, and Stereodynamics" *J. Org. Chem*. **2008**, *73*, 2811–2818. (b) The characterization of 2-isopropylbenzaldehyde was the same as the literature report. Nate, H.; Sekine, Y.; Honma, Y.; Nakai, H.; Wada, H.; Takeda, M.; Yabana, H.; Nagao, T. "Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. I. 2-Phenylthiazolidine-3-thiocarboxamides" *Chem. Pharm. Bull*. **1987**, *35*, 1953–1968.

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

[4] Smith, D. J.; Yap, G. P. A.; Kelley, J. A.; Schneider, J. P. "Enhanced Stereoselectivity of a Cu(II) Complex Chiral Auxiliary in the Synthesis of Fmoc-l-γ-carboxyglutamic Acid" *J. Org. Chem*. **2011**, *76*, 1513–1520.

[5] Shaikh, N. S.; Junge, K.; Beller, M. "A Convenient and General Iron-Catalyzed Hydrosilylation of Aldehydes" *Org. Lett*. **2007**, *9*, 5429–5432.

[6] Diogo, H. P.; Pinto, S. S.; Moura Ramos, J. J. "Thermal Behaviour and Slow Molecular Mobility in Two Isomers of Biphenylmethanol" *J. Therm. Anal. Calorim*. **2006**, *83*, 361–366.

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

[8] Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. "Cobalt-Catalyzed Aryl-Sulfur Bond Formation" *Org. Lett*. **2006**, *8*, 5613–5616.

[9] Joseph, R.; Masson, E. "Subtle "Supramolecular Buttressing Effects" in Cucurbit[7]uril/Guest Assemblies" *Org. Biomol. Chem*. **2013**, *11*, 3116–3127.

[10] Knowles, D. B.; Lin, C.; Mackenzie, P. B.; Tsai, J.-Y.; Walters, R.; Beers, S. A.; Brown, C. S.; Yeager, W. H.; Barron, E. "Blue Phosphorescent Iridium Complexes and Light-Emitting Devices Using Them" Universal Display Corporation USA, WO 2008156879, **2008**.

[11] Aguilar, N.; Fernandez, J. C.; Terricabras, E.; Carceller Gonzalez, E.; Salas Solana, J. "Preparation of Substituted Tricyclic Compounds with Activity towards EP1 Receptors" Almirall, S.A., Spain; Draconis Pharma, S.L.; Laboratorios Del Dr. Esteve, S.A., WO 2013149997, **2013**.

[12] Zhang, H.-H.; Bonnesen, P. V.; Hong, K. "Palladium-Catalyzed Br/D Exchange of Arenes: Selective Deuterium Incorporation with Versatile Functional Group Tolerance and High Efficiency" *Org. Chem. Front*. **2015**, *2*, 1071–1075.