Synthesis of Electron-Rich β-Fluoroamines: Alkene Aminofluorination Using *N*,*N*-Dialkylhydroxylamines

by

Colton Kawika Sam Ku

Department of Chemistry
Duke University

Date:_____

Approved:

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Qiu Wang, Supervisor

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Steven J. Malcolmson

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Aaron D. Franklin

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Department of
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2019

ABSTRACT

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Abstract

Fluorine in modern pharmaceuticals has enabled development of drugs with enhanced therapeutic value through the selective modulation of a variety of pharmacological parameters. Therefore, methods to prepare molecular scaffolds which contain the fluorine atom are of critical importance for the continued success of novel drug discovery. In this thesis, the regioselective intermolecular aminofluorination of alkenes has been achieved with *N*,*N*-dialkylhydroxylamines and nucleophilic fluorine. With this copper-catalyzed approach, a variety of pharmaceutically relevant β-fluorophenethylamines have been prepared. Additionally, through the systematic evaluation of substituted alkenes and electronically varied *O*-substituted-*N*-hydroxylmorpholines, the limitations of the method have been discovered. Mechanistic experiments have also revealed the presence of a radical intermediate, which suggests the transformation occurs through a nitrogen-initiated pathway.

Dedicated to the memory of

Ried Kapō Ku

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Abbreviations

2-MeTHF	2-methyltetrahydrofuran
5HT	5-hydroxytryptamine
Ac	acetyl
acac	acetylacetone
Ar	aryl
B_2pin_2	bis(pinacolato)diboron
BC	bathocuproine
BHT	butylated hydroxytoluene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binapthyl
Boc	*tert*-butyloxycarbonyl
BPO	benzoyl peroxide
Bz	benzoyl
CBz	carboxybenzyl
DCE	1,2-dichloroethane
Diphos	1,2-bis(diphenylphosphino)ethane
DME	1,2-dimethoxyethane
DMEDA	1,2-dimethylethylenediamine
DMF	dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane)
dr	diastereomeric ratio
dtbbpy	4,4′-di-*tert*-butyl-2,2′-dipyridyl
eh	2-ethylhexanoate
ESI	electron spray ionization
Et	ethyl
$Et_3N{\cdot}3HF$	triethylamine trihydrofluoride
EtOH	ethanol
FEP	fluorinated ethylene propylene
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography

HRMS	high-resolution mass spectrometry
IR	infrared
kcal	kilocalorie
Log P	logarithm of partition coefficient
Me	methyl
MeCN	acetonitrile
MHz	megahertz
MsOH	methanesulfonic acid
^{n}Bu	normal butyl
ND	not detected
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NR	no reaction
Ph	phenyl
phen	phenanthroline
pK_a	negative logarithm of acid dissociation constant
PPTS	pyridinium *para*-toluenesulfate
ppy	2-phenylpyridine
Py	pyridine
SEGPhos	4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane)
SET	single electron transfer
S_N2	2nd order nucleophilic substitution
TBAF	tetra-*n*-butylammonium fluoride
^{t}Bu	*tert*-butyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Acknowledgements

My appreciation and sincerest gratitude go to the many who have supported my development to this point. First and foremost, thank you to my parents, Ryne and MaeJean, for their unending love and guidance, and to my siblings, Jade, Kristy, Nolan, and Clayton for always having my back. In addition, I've had the good fortune of being mentored by multiple amazing individuals along the way, namely: Prof. Asmik Oganesyan, Prof. Mark J. Kurth, Prof. Qiu Wang, Dr. Chuan Liu, and Dr. Brett N. Hemric. Thank you for believing in my potential and offering me so much in the brief times we've shared together.

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1. Introduction

1.1 Significance of Fluorine in Modern Pharmaceuticals

In 1955, the first fluorine-containing drug, fludrocortisone, was approved by the U.S. Food and Drug Administration.[1] By 1997, the maturation of fluoro-organic synthetic methodology had enabled over 1,500 fluorinated compounds to reach commercial success.[2] It is estimated that 30% of all newly approved drugs contain at least one fluorine atom.[3] Considering the virtually complete absence of fluorine in naturally occurring organic molecules,[4] an obvious question emerges: What are the reasons behind the ever increasing number of fluorine-containing drugs?

The preponderance of fluorine in modern pharmaceuticals can be understood by the beneficial physiochemical changes which result from fluorine substitution on bioactive molecules. The added electronegativity and hydrogen bonding capability of fluorine, coupled with its minimal steric influence, have been shown to impart beneficial pharmacological parameters to a wide variety of biologically relevant compounds.[5] Metabolic stability, basicity, polarity, conformational orientation, and protein binding are some of the many factors which can be readily modulated through the judicious substitution of a fluorine atom. For example, in a study on increasing the bioavailability of $5HT_{2A}$ antagonists, Rowley and colleagues showed the installation of a fluorine on the piperidine ring decreased the pK_a of the conjugate acid from 10.4 to 8.5 (Figure 1, A).[6] This drop in basicity resulted in a substantial increase in bioavailability.

Fluorine substitution has also proven effective in altering the fat solubility of small molecules. As demonstrated by Linclau et. al., 2,2,2-trifluorination of ethanol significantly increases its lipophilicity (Figure 2, B).[7] Furthermore, a pronounced gauche-effect is observed for alkyl-organofluorines. Although one might expect the anti-conformation of 1,2-difluoroethane to be more favored due to steric effects, the stabilizing $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ interactions supported by the gauche conformer enable its relative stability by 0.5–0.9 kcal/mol (Figure 1, C).[8] Recent studies indicate this gauche effect can greatly impact the binding affinity of fluorinated HIV protease inhibitors through

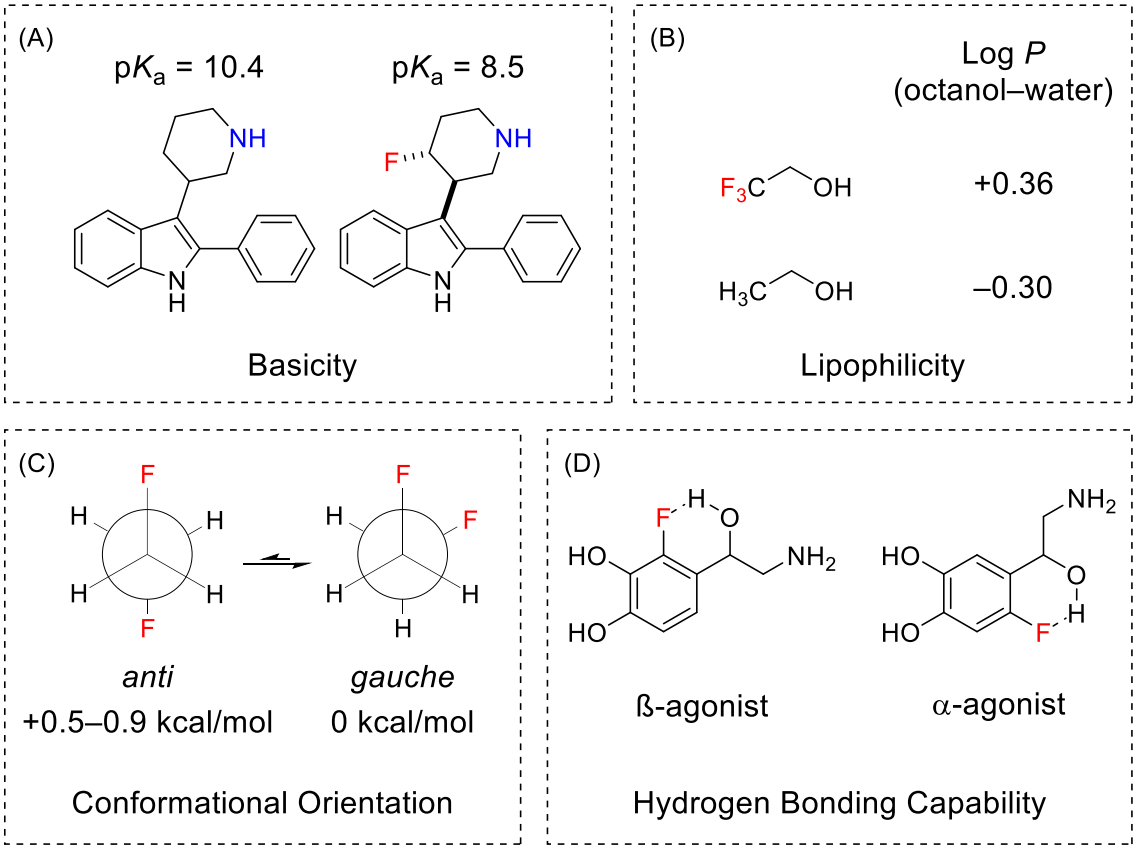


Figure 1: Modulation of molecular properties through fluorine substitution.

stabilization of the fully extended carbon backbone.[9] Finally, fluorine's ability to hydrogen bond has been leveraged in many efforts toward lead optimizations.[10] One extreme example was discovered through the study of constitutional isomers of fluorinated norepinephrine. Two distinct conformations, enabled by C–F···H–O intramolecular interactions, resulted in the 2-fluoro and 6-fluoro analogues displaying markedly contrasting binding affinities (Figure 1, D).[11]

1.2 Importance of Alkene Aminofluorination

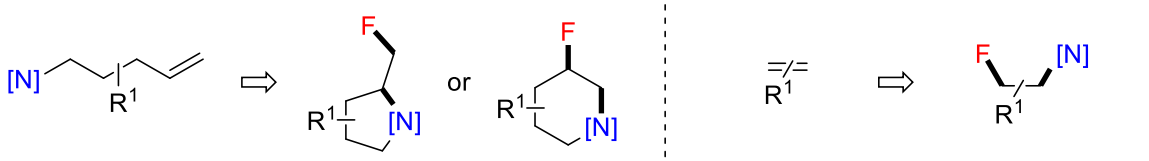
The enhanced therapeutic value that the fluorine substituent offers to modern medicine is unequivocal. And yet, the relatively low number of reported organofluorine methodologies limit both the diversity and convenient syntheses of many potential drug candidates.[12] To support the continued success of drug discovery, great importance has been placed on the development of novel methods to access organofluorines.

As installation of a fluorine atom vicinal to an amine has been shown to beneficially increase the bioavailability of nitrogen-containing therapeutics,[13] the β-fluoroamine scaffold has been recognized as an important synthetic target. Therefore, it is without surprise that there now exists a number of potential routes to access β-fluoroamines.[14] Of them, the difunctionalization of simple alkenes offers the ability to rapidly generate molecular complexity in a single step using feedstock chemicals. Consequently, several alkene aminofluorination strategies have recently emerged through a number of varying mechanistic approaches.[15]

1.3 Representative Examples of Previous Intermolecular Alkene Aminofluorination Methods

A large body of work has been established on alkene aminofluorination methodology. However, the vast majority of these methods utilize intramolecular cyclizations as a means for amination.[15] While synthetically useful in their own right, these methods are limited by the lack of structural diversity they can generate (Scheme 1, A). In contrast, three-component intermolecular aminofluorination transformations permit the use of a wide variety of alkene starting materials and are amenable to the generation of acyclic β-fluoroamines (Scheme 1, B). The focus of this thesis is therefore placed on the exclusive development of intermolecular aminofluorination of simple alkenes.

Scheme 1: Intramolecular vs intermolecular alkene aminofluorinations.

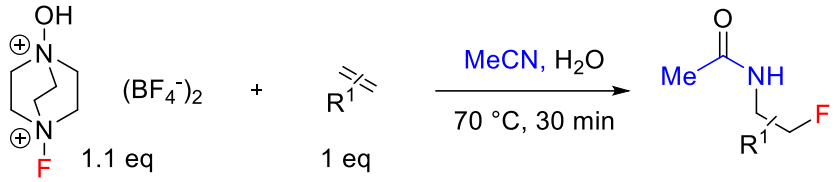


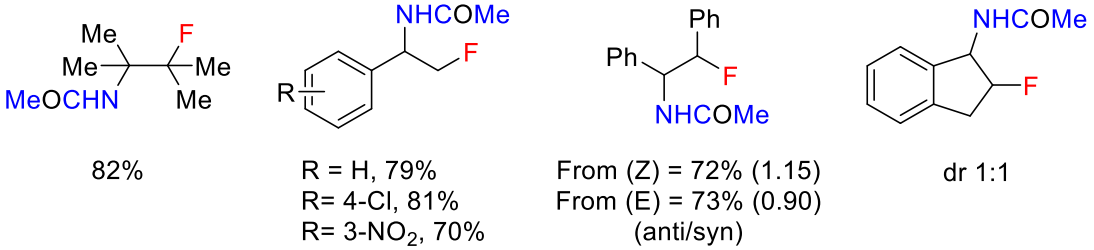
(A) Intramolecular Aminofluorinations (B) Intermolecular Aminofluorinations

1.3.1 Alkene Aminofluorination Through Electrophilic Fluorination

The first direct aminofluorination was achieved by Stavber et al. in 1996 utilizing an electrophilic fluorine salt. A β-fluorocarbocation intermediate was proposed to form upon addition to an alkene, followed by a Ritter-type nucleophilic addition to afford the product as a single regioisomer and 1:1 mixture of diastereomers (Scheme 2). [16-18]

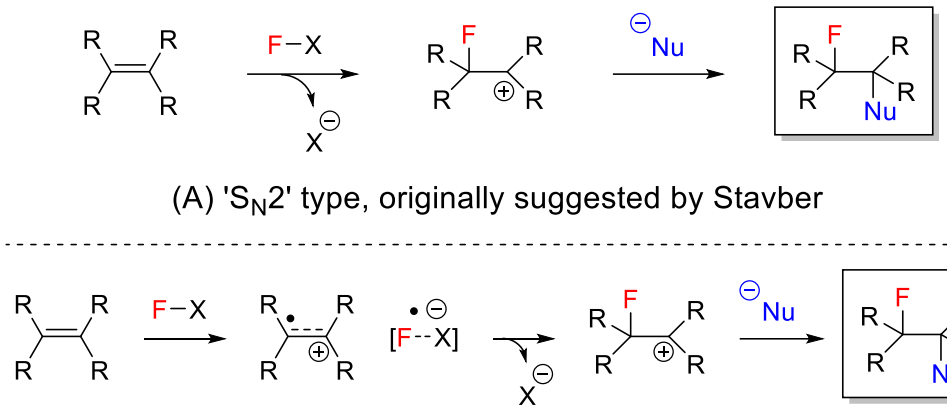
Scheme 2: Intermolecular alkene aminofluorination via electrophilic fluorination.





Exploration of the substrate scope revealed the transformation was effective in the functionalization of both aryl- and alkyl-substituted alkenes and could even transform sterically congested 1,1,2,2-tetramethylethene in good yield. This strategy was later extended to nucleophilic triazoles[19] and for the preparation of α-trifluoromethylbenzylamines from β,β-difluorostyrenes.[20] It should be noted that a later mechanistic study of this electrophilic fluorine-initiated aminofluorination reaction has indicated the strong likelihood of the transformation proceeding through a radical cation intermediate (Scheme 3, B), as opposed to the direct cation intermediate formation initially proposed by Stavber (Scheme 3, A).[21] This conclusion was made after ESI-MS and ESI-MS/MS experiments explicitly detected the mass of the radical cation intermediate under the reaction conditions.

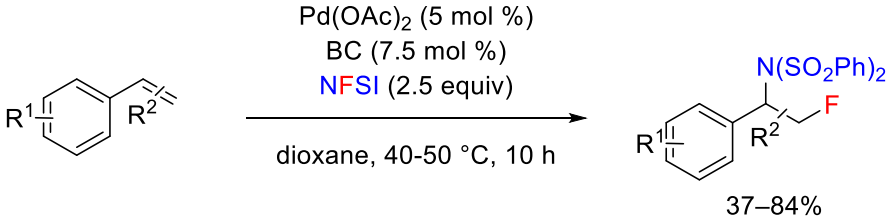
Scheme 3: Original and updated proposed mechanisms for electrophilic fluorine-initiated alkene aminofluorination.



1.3.2 Palladium-Catalyzed Intermolecular Alkene Aminofluorination

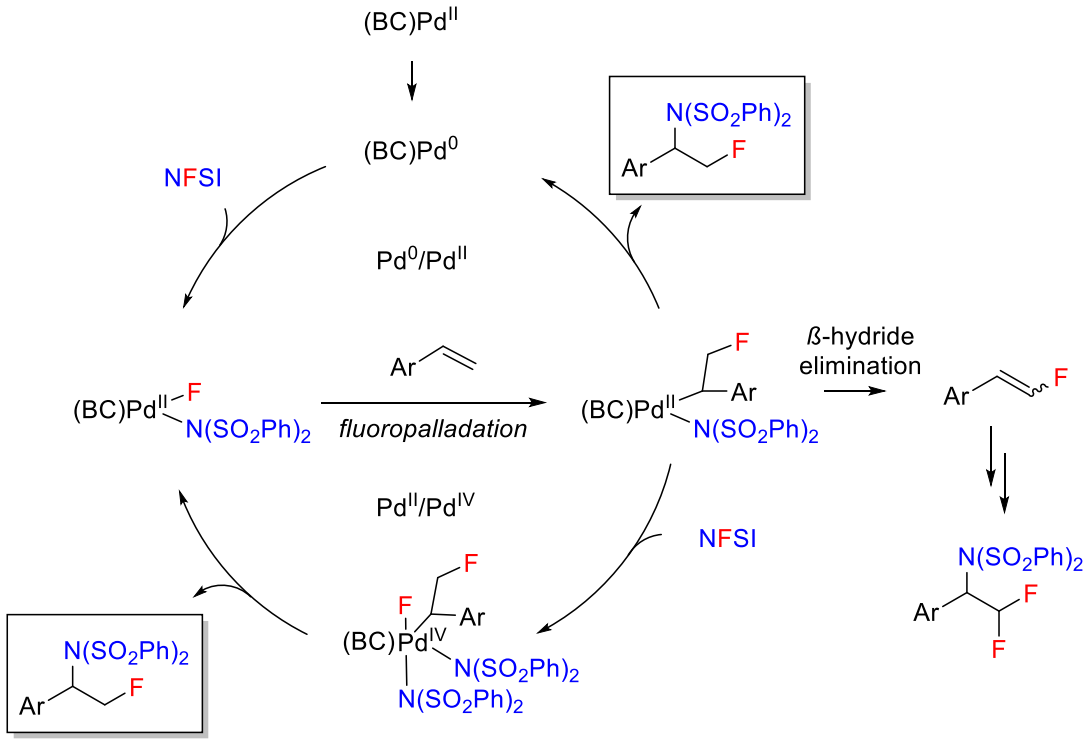
The use of palladium as a transition metal catalyst for aminofluorination was initially pioneered by the Liu group in 2009.[22-24] In their intermolecular aminofluorination of styrenes,[25] *N*-fluorobenzenesulfonimide (NFSI) served as both the amine and fluoride source to generate 2-fluoro-1-phenyl-1-ethanamines in a regioselective fashion (Scheme 4). In the proposed mechanism, fluoropalladation was invoked as the key carbon–fluorine bond-forming step in either a Pd^{0}/Pd^{II} or Pd^{II}/Pd^{IV} catalytic cycle, followed by reductive elimination to form the carbon–nitrogen bond. The

Scheme 4: Palladium-catalyzed aminofluorination of styrenes.



unexpected 1,1-difluoro-2-amino trifunctionalized product was also observed in low yield, which the authors rationalized could have arisen from the β-hydride elimination product (β-fluorostyrene) (Scheme 5).

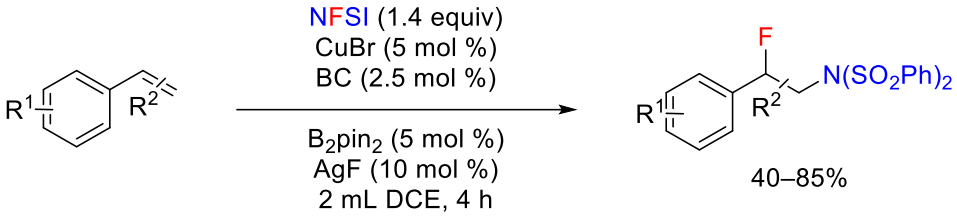
Scheme 5: Proposed mechanism for palladium-catalyzed intermolecular aminofluorination of styrenes.



1.3.3 Copper-Catalyzed Intermolecular Alkene Aminofluorination

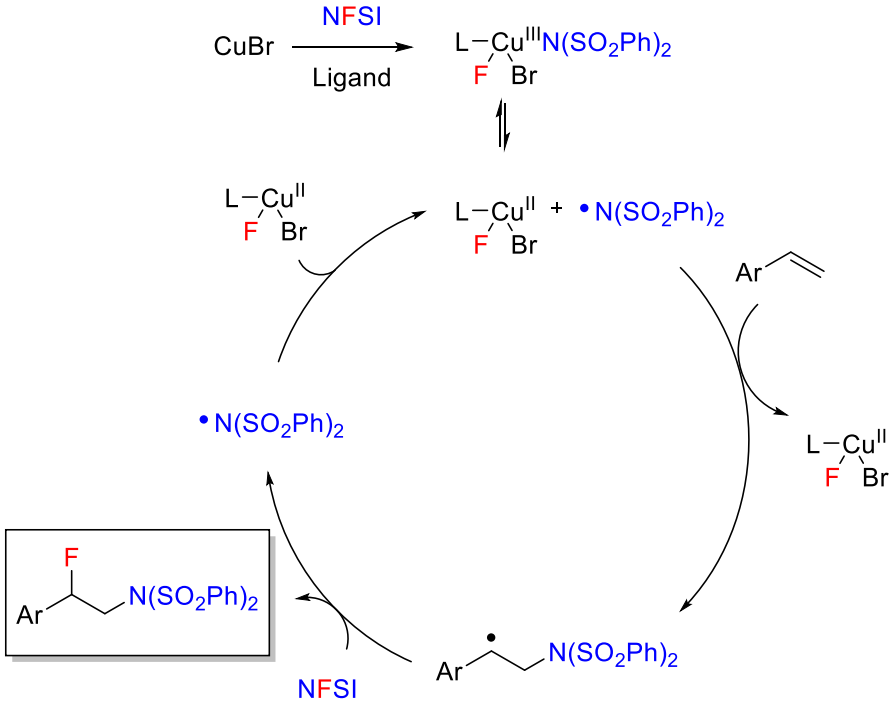
Copper-catalyzed styrene aminofluorinations achieve the regioselective reverse of the analogous palladium-catalyzed transformation due to the propensity of copper to undergo a single electron transfer (SET) pathway. The Zhang[26] and Perez[27] groups have independently developed an alkene aminofluorination strategy which leverage a copper-based catalyst. In Zhang's transformation, NFSI was used as both the

Scheme 6: Copper-catalyzed aminofluorination of styrenes.



amine and fluoride source, while AgF and a lewis acid, bis(pinacolato)diboron (B_2pin_2), were found necessary to remove halide ions and improve the overall yield (Scheme 6).

Scheme 7: Proposed mechanism for copper-catalyzed intermolecular aminofluorination of alkenes.



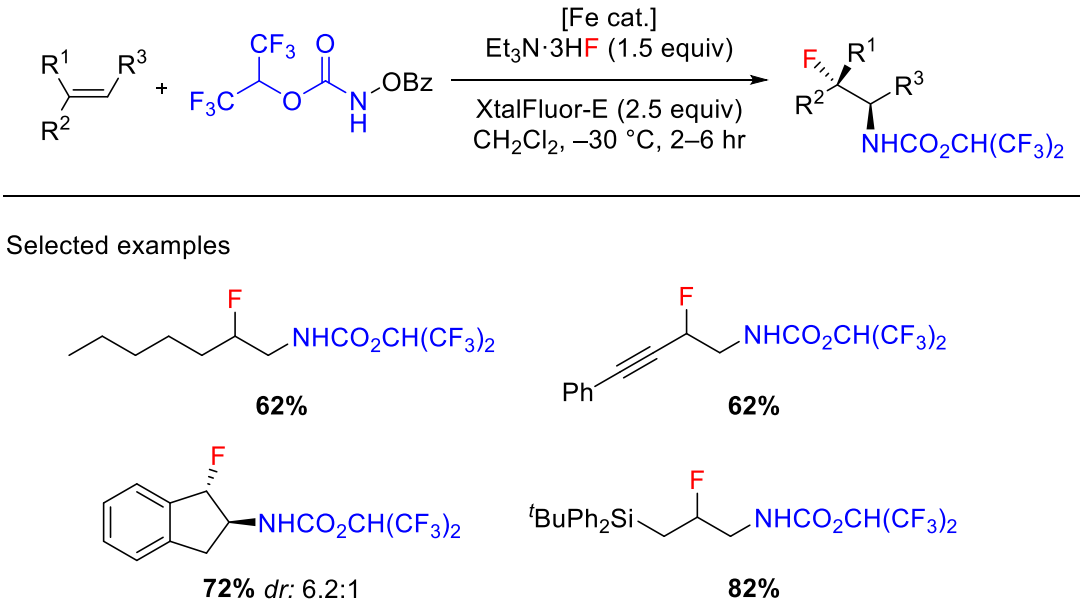
Supported by both TEMPO trapping and radical clock cyclopropyl ring opening experiments, a nitrogen-initiated mechanism was proposed (Scheme 7). Copper(I) could first oxidatively add to NFSI, then homolytically cleave to generate a nitrogen-centered

radical. After olefin addition, the formed carbon-centered radical could abstract fluorine from a second molecule of NFSI to afford the product while regenerating another nitrogen-centered radical in a cascading manner. Regioselectivity was rationalized to arise due to the carbon-centered radical's stability at the benzylic position.

1.3.4 Iron-Catalyzed Intermolecular Alkene Aminofluorination

The H. Xu group successfully utilized iron as a transition metal catalyst to achieve intermolecular alkene aminofluorination with a substantially expanded substrate scope relative to previous methods.[28] A very specific mixture of fluoride sources permitted fluorine to serve as a nucleophile without attacking the iron center and deactivating the catalyst. This specially tailored system proved so selective that even

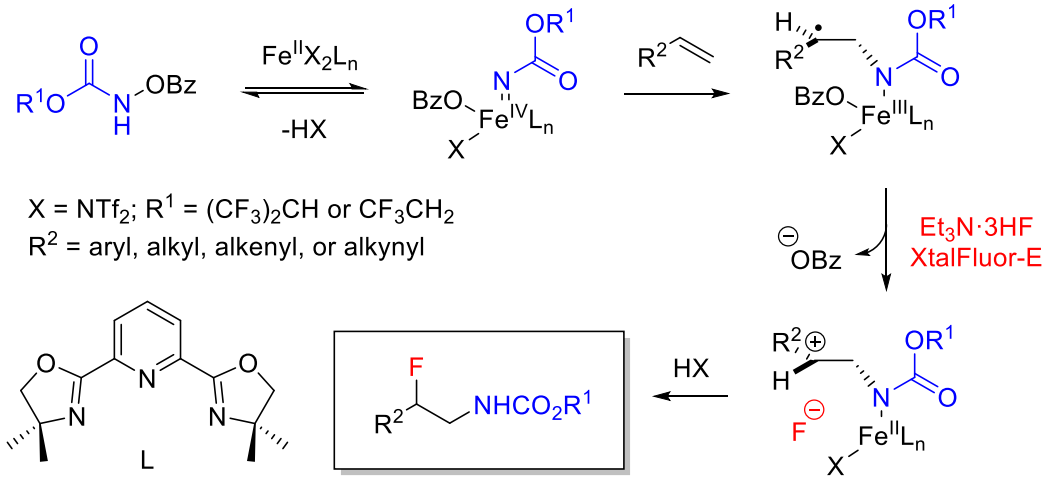
Scheme 8: Iron-catalyzed aminofluorination of alkenes.



silyl-containing alkenes were able to undergo aminofluorination without desilylation (Scheme 8). Enynes, aliphatic alkenes, and substituted alkenes were also found effective in the transformation.

The authors proposed a pathway involving the formation of an iron-nitrenoid intermediate (Scheme 9). Iron(II) could first oxidatively insert to the N–O bond of the hydroxylamine ester, and after deprotonation, form the nitrenoid. The nitrenoid would then combine with an alkene via radical addition, which could go on to react through a SET with high-valent iron(III) to generate a carbocation. The carbocation would quickly be attacked by nucleophilic fluoride, and the desired product could be generated after protonolysis of the iron–nitrogen bond.

Scheme 9: Proposed mechanism for iron-catalyzed intermolecular aminofluorination of alkenes.

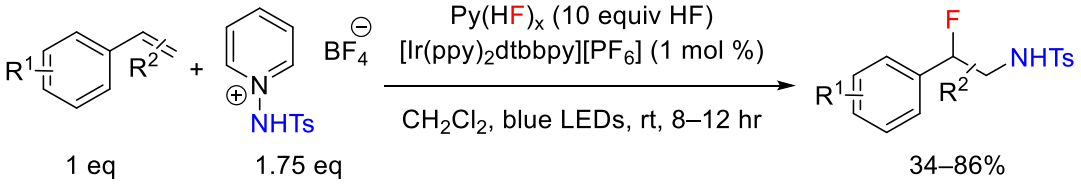


1.3.5 Photocatalyzed Intermolecular Alkene Aminofluorination

Finally, three-component intermolecular alkene aminofluorination has also been

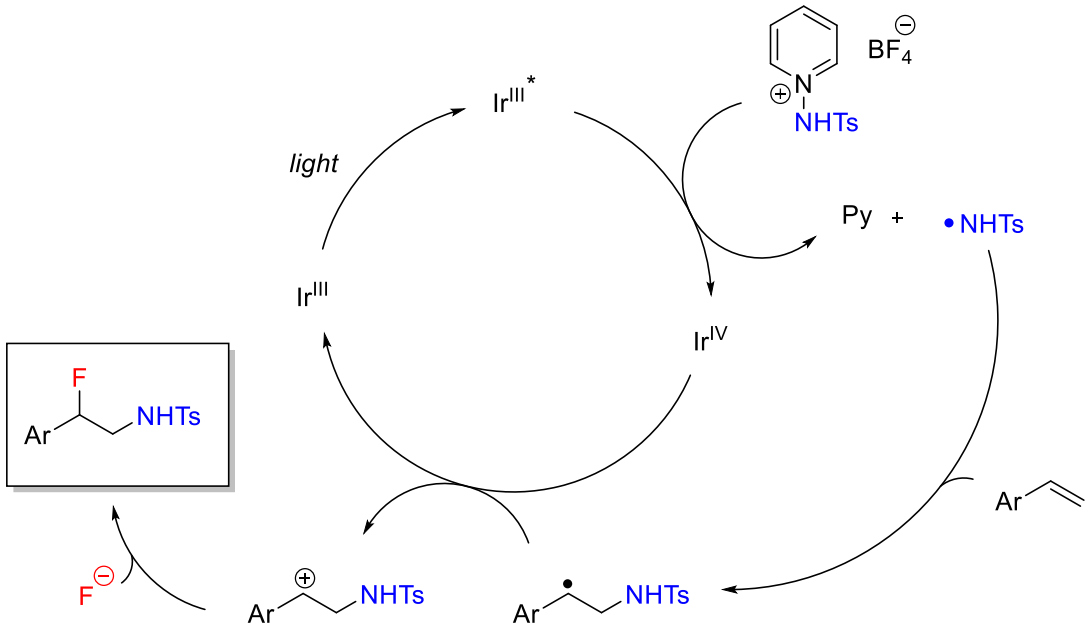
accomplished using a photocatalyzed approach. In 2018, P. Xu and associates disclosed the regioselective aminofluorination of styrenes which relied upon visible-light photoexcitation of an iridium catalyst to generate β-fluoroamines (Scheme 10).[29]

Scheme 10: Photocatalyzed aminofluorination of styrenes.



As TEMPO trapping experiments completely inhibited the reaction, the authors suggested the transformation could occur through a radical pathway. First, visible light could generate the excited iridium(III) species, which could then be oxidatively quenched by the aminopyridine salt to generate the nitrogen-centered radical and a

Scheme 11: Proposed mechanism for photocatalyzed intermolecular aminofluorination of styrenes.



strongly oxidizing iridium(IV) species. The nitrogen-centered radical could then react with an alkene through a radical addition, while the resulting carbon-centered radical could be oxidized to a carbocation by iridium(IV). Nucleophilic fluoride could then attack the carbocation to generate the desired β-fluoroamine.

1.4 Deficiencies of Previous Methods

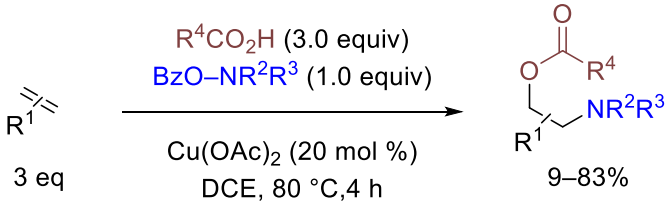
Despite the great advancements in intermolecular alkene aminofluorination strategies, past methods only permit the installation of electron-deficient carbamate or sulfonamide type amines. The direct installation of electron-rich alkylamines remains an unmet challenge. If accomplished, the *N*-alkylaminofluorination of alkenes would allow the facile preparation of β-fluoroamines which are currently inaccessible by this reaction manifold.

2. Copper-Catalyzed Aminofluorination with *N,N*-Dialkyl-hydroxylamines

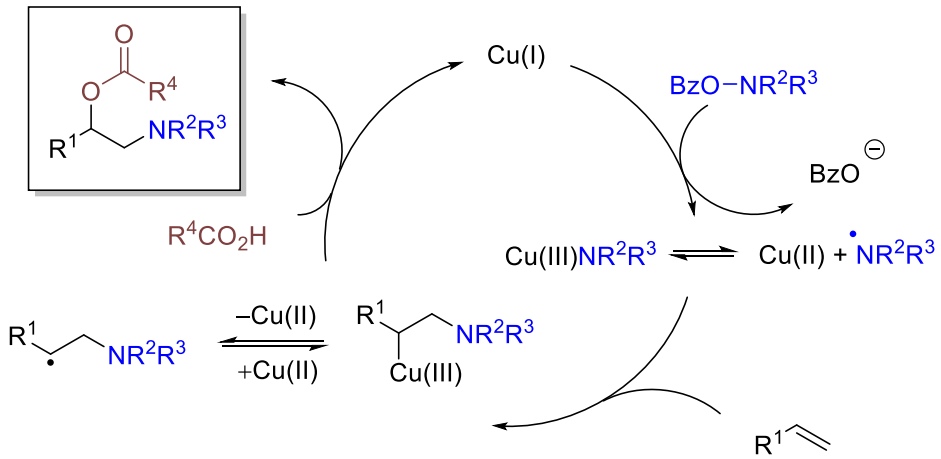
2.1 Initial Inspiration and Strategy

We envisioned that alkene aminofluorination could be realized using electrophilic *O*-benzoyl-*N,N*-dialkylhydroxylamines and nucleophilic fluorine. The use of these robust nitrogen precursors[30, 31] was initially inspired by the related work of alkene aminooxygenation pioneered by our lab (Scheme 12).[32, 33] As mechanistic studies with both TEMPO trapping and radical clock cyclopropyl ring-opening experiments revealed a pathway in which the electrophilic amine initiated the addition to the alkene (Scheme 13), it stood reasonable that a change in the nucleophile for the final 'trapping' step would leave the catalytic cycle unaffected and in theory be possible. Namely, if a compatible nucleophilic fluoride source could be used instead of an oxygen nucleophile, the original goal of *N*-alkylaminofluorination could be achieved.

Scheme 12: Intermolecular alkene aminooxygenation with *N,N*-dialkyl-hydroxylamines and carboxylic acids.



Scheme 13: Proposed mechanism of copper-catalyzed intermolecular aminooxygenation of alkenes.

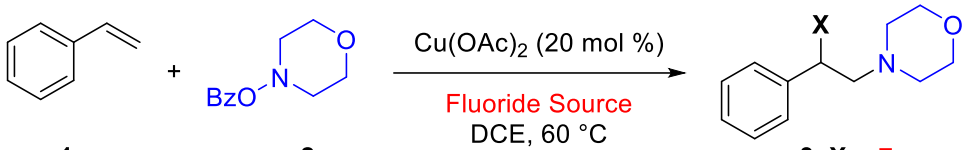


2.2 Results and Discussion

2.2.1 Screening for Optimal Conditions

To probe the initial hypothesis that electron rich β-fluoroamines could be synthesized via alkene 1,2-aminofluorination, styrene 1 was subjected to *O*-benzoyl-*N*-hydroxylmorpholine 2 in the presence of various fluorinating agents (Table 1). Screening of fluoride sources such as Olah's reagent, silver fluoride, cesium fluoride, and tetrabutylammonium fluoride provided no detectable desired product (entries 1–4). When triethylamine trihydrofluoride was employed (entry 5), the desired product was excitingly observed in low yield along with undesired aminooxygenation side product 4. In an attempt to modulate the nucleophilicity of the fluoride complex[34] and outcompete the benzoate, various stoichiometries of the triethylamine hydrofluoride were prepared and tested. Surprisingly, triethylamine hydrofluoride complexes with stoichiometries varying from 1:3, such as entries 6–9, failed to produce the desired product

Table 1: Screening of fluoride source.[a]



1 **2** **3, X** = F **4, X** = OBz

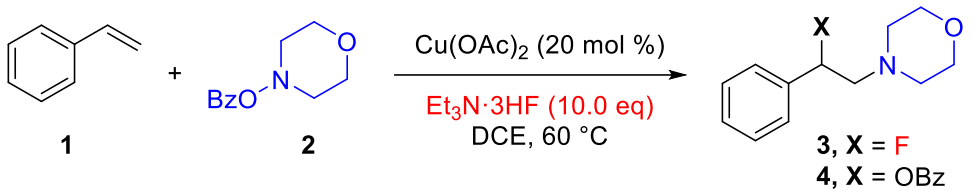
entry	fluoride source	fluoride (equiv)	**3** (%)[b]	**4** (%)[c]
1	$Py(HF)_x$	3.0	0	0
2	AgF	3.0	0	0
3	CsF	3.0	0	3
4	TBAF	3.0	0	0
5	$Et_3N•3HF$	3.0	22	12
6	$Et_3N•HF$	3.0	0	0
7	$Et_3N•2HF$	3.0	0	0
8	$Et_3N•4HF$	3.0	trace	trace
9	$Et_3N•5HF$	3.0	trace	trace
10	$Et_3N•3HF$	5.0	36	8
11	**$Et_3N•3HF$**	**10.0**	**36 (35)[d]**	**5**

[a]Reaction conditions: 10-mL sealed FEP tube, **1**, (0.6 mmol, 3.0 equiv), **2** (0.2 mmol, 1.0 equiv), DCE (1.0 mL). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard. [c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [d]Isolated yield.

in any isolable amount. This illustrated the unique efficacy of the triethylamine trihydrofluoride complex for the transformation. Optimization of the procedure was next studied by varying the fluoride equivalents (entries 10–11). An improvement in yield could be achieved if an excess of five equivalents of triethylamine trihydrofluoride was employed, so the conditions for entry 11 were elected for further study.

Next, the alkene and hydroxylamine starting materials were varied to determine the optimal loading amounts of both reagents (Table 2). When styrene is held as the limiting reagent, yields are generally low (entries 1–3). It should be noted that increasing

Table 2: Screening of alkene and hydroxylamine equivalents.[a]



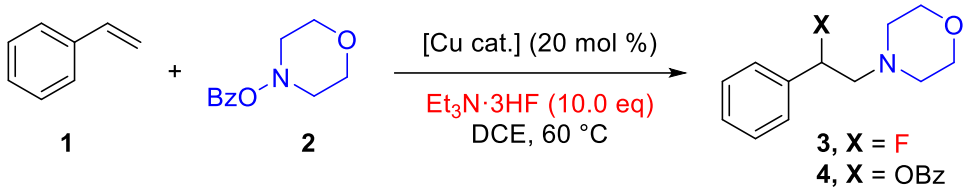
entry	**1** (equiv)	**2** (equiv)	**3** (%)[b]	**4** (%)[c]
1	1.0	1.0	17	5
2	1.0	2.0	19	8
3	1.0	3.0	18	10
4	**2.0**	**1.0**	**42**	**4**
5	3.0	1.0	36	5

[a]Reaction conditions: 10-mL sealed FEP tube, DCE (1.0 mL). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard. [c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

the hydroxylamine loading had a direct effect on the amount of benzoate trapped side product (4) formed in the reaction. For those reasons, the hydroxylamine was held as limiting in the transformation. Exceeding 2.0 equivalents of the alkene also resulted in a slight drop in yield, so the conditions for entry 4 were chosen for further optimization.

Various copper catalysts were screened in the reaction condition to further optimize the yield of the desired product. Copper(I) and copper(II) salts produced identical yields, which seemed to suggest that a disproportionation event could have occurred to generate the same reactive metal species. Copper(II) chloride, copper(I) chloride, and copper(I) iodide all reacted poorly in the reaction conditions, but copper(II) fluoride gave a similar result to the standard copper(II) acetate (entry 11). To determine if the copper fluoride species was the active fluorinating source, a control was run (entry 12) in which copper(II) fluoride was reacted without addition of triethylamine

Table 3: Screening of copper catalyst.[a]

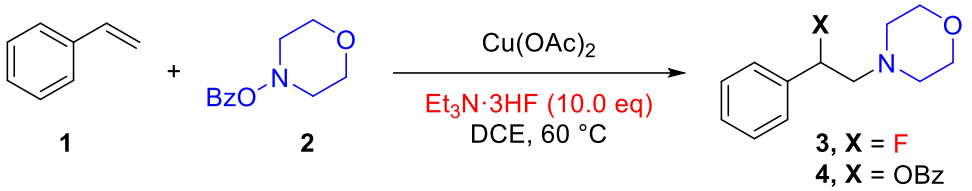


entry	copper	change in condition	**3** (%)[b]	**4** (%)[c]
1	CuOAc	-	41	3
2	**$Cu(OAc)_2$**	**-**	**41**	**3**
3	CuOTf	-	38	2
4	$Cu(OTf)_2$	-	41	2
5	$Cu(eh)_2$	-	39	3
6	$Cu(acac)_2$	-	37	3
7	$Cu(MeCN)_4BF_4$	-	36	2
8	$CuCl_2$	-	13	1
9	CuCl	-	24	2
10	CuI	-	3	1
11	CuF_2	-	39	2
12	CuF_2 (100 mol %)	no Et_3N•3HF added	2	28
13	-	no copper catalyst	0	0

[a]Reaction conditions: 10-mL sealed FEP tube, **1** (0.4 mmol, 2.0 equiv), **2** (0.2 mmol, 1.0 equiv), DCE (1.0 mL). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard. [c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

trihydrofluoride. The product **3** was observed in a trace amount, which suggests that copper(II) fluoride could be directly participating in the reaction condition. Unfortunately, the excessive benzoate background reactivity consumed much of the limiting reagent, which makes reaching a conclusion about the nature of copper(II) fluoride difficult. Finally, as an additional control, copper catalyst was entirely removed from the system (entry 13), and neither 3 nor 4 were detected in the crude reaction mixture. Copper(II) acetate was chosen for continued study as no other catalyst gave an increased yield.

Table 4: Screening of catalyst loading.[a]

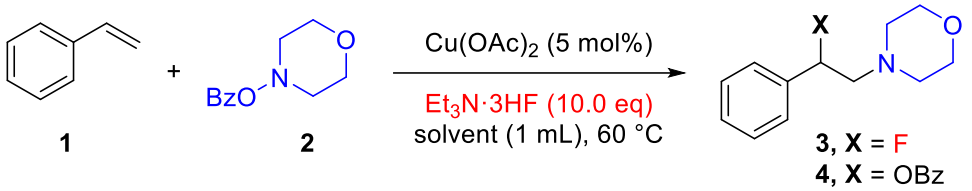


entry	$Cu(OAc)_2$ (mol %)	**3** (%)[b]	**4** (%)[c]
1	1 mol %	39	3
2	**5 mol %**	**44**	**3**
3	10 mol %	41	3
4	20 mol %	41	3
5	30 mol %	39	3

[a]Reaction conditions: 10-mL sealed FEP tube, **1** (0.4 mmol, 2.0 equiv), **2** (0.2 mmol, 1.0 equiv), DCE (1.0 mL). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard. [c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

Screening of the copper catalyst amount revealed that the transformation could be performed with relatively low loading (Table 4). Between the chosen values, 5 mol % of the copper(II) acetate catalyst gave a slight increase over the previous amount, and was thus chosen for further study.

Table 5: Screening of solvent.[a]



entry	solvent	**3** (%)[b]	**4** (%)[c]
1	DME	trace	trace
2	dioxane	6	trace
3	2-MeTHF	2	trace
4	$CF_3C_6H_5$	4	trace
5	**DCE**	**37**	**2**
6	toluene	trace	trace
7	EtOH	trace	ND
8	DMF	trace	1
9	MeCN	24	2

[a]Reaction conditions: 10-mL sealed FEP tube, **1** (0.4 mmol, 2.0 equiv), **2** (0.2 mmol, 1.0 equiv). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard. [c]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

Varying the solvent had a large effect on the reaction (Table 5). Ethereal solvents such as DME, dioxane, and 2-MeTHF were not suitable for the reaction. In addition, trifluoromethylbenzene, toluene, ethanol, and dimethylformamide completely inhibited product formation. DCE and MeCN were uniquely able to generate the product in an isolable amount, but DCE outperformed MeCN to a large degree. With this information in hand, DCE was chosen as the optimal solvent for the aminofluorination reaction.

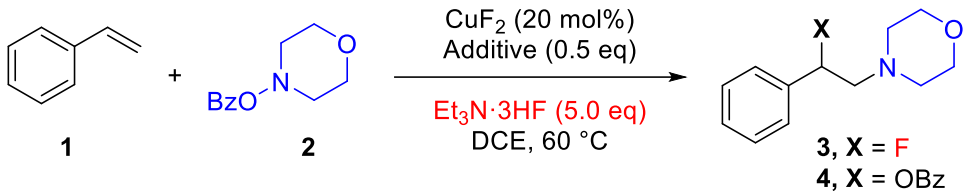
Table 6: Screening of ligand.[a]

entry	ligand	ligand mol %	**3** (%)[b]	**4** (%)[b]
1	none	-	31	6
2	2,2′-bipyridyl	20 mol %	10	2
3	1,10-phen	20 mol %	27	9
4	PPh_3	40 mol %	6	10
5	SEGPhos(S)	20 mol %	24	13
6	BINAP(±)	20 mol %	2	1
7	Xphos	40 mol %	8	4
8	Diphos	20 mol %	22	9
9	Xantphos	20 mol %	16	12
10	dppp	20 mol %	21	10
11	dppb	20 mol %	12	9
12	DMEDA	20 mol %	6	3

[a]Reaction conditions: 1-dram vial, **1** (0.6 mmol, 3.0 equiv), **2** (0.2 mmol, 1.0 equiv). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

In a different set of conditions, various ligands were tested in the aminofluorination reaction (Table 6). Nitrogen heterocyclic ligands such as 2,2′-bipyridyl and 1,10-phenanthroline, as well as Buchwald- and other phosphine-based ligands resulted in no beneficial increase in yield. Counter to the desired effect, in certain cases (entries 3–5 and 8–11) an observed increase in benzoate trapped side product occurred. With the information that the tested ligands had no beneficial effect to the transformation, we concluded that the reaction was best run without an externally added ligand.

Table 7: Screening of additives.[a]

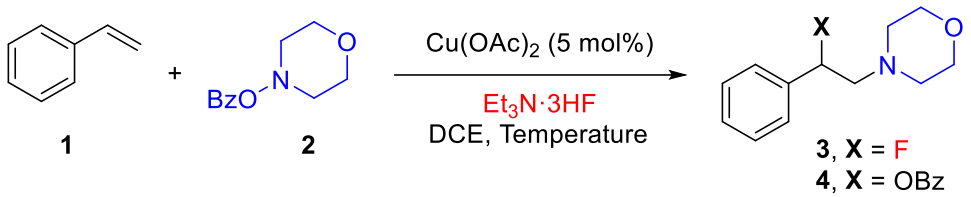


entry	additive	**3** (%)[b]	**4** (%)[b]
1	-	30	5
2	pyridine	6	6
3	HFIP	10	19
4	PPTS	7	5
5	formic acid	8	11
6	$TsOH•H_2O$	11	20
7	MsOH	20	18
8	NaH_2PO_4	ND	ND
9	Cs_2CO_3	trace	trace
10	K_2CO_3	6	5
11	K_3PO_4	ND	ND

[a]Reaction conditions: 1-dram vial, **1**, (0.6 mmol, 3.0 equiv), **2** (0.2 mmol, 1.0 equiv). Time of reaction was 18 hours until **2** consumption. [b]Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

In addition to varying the reaction's parameters for condition optimization, multiple additives were tested for beneficial effects toward the product yield (Table 7). Organic bases and acids were first examined, and it was discovered that addition of either decreased the yield substantially. Unfortunately, most inorganic bases examined also either completely inhibited or severely reduced the desired yield of 3. Therefore, the optimal condition was determined as additive-free.

Table 8: Screening of temperature and fluoride equivalents.[a]



entry	temperature (°C)	$Et_3N{\cdot}3HF$ (equiv)	time (h)	**3** (%)[b]	**4** (%)[b]
1	room temp	10.0	>72	NR	-
2	40	10.0	38	11	1
3	50	10.0	24	39	2
4	60	10.0	18	42	3
5	60	20.0	18	40	trace
6	80	10.0	2	37	3
7	**80**	**20.0**	**2**	**39 (38)**[c]	**trace**
8	100	10.0	0.5	24	3

[a]Reaction conditions: 10-mL sealed FEP tube, **1**, (0.4 mmol, 2.0 equiv), **2** (0.2 mmol, 1.0 equiv). Time of reaction was until **2** consumption. [b]Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [c]Isolated yield.

Finally, we ran a series of experiments to determine the optimal temperature in which the reaction could take place (Table 8). At lower temperatures, the hydroxylamine reacts very slowly and as a result did not produce any alkene functionalized products at room temperature (entry 1). When the temperature is increased, the yields of both aminofluorination and aminooxygenation products increase accordingly. Although the previously optimized condition (entry 4) produced the highest yield, the extended time of the reaction and production of benzoate-trapped side product made it less than ideal. To shorten the reaction time, the temperature was increased to 80 °C, and to remove the benzoate-trapped side product, 20.0 equivalents of the fluorinating reagent was utilized. Thus, the conditions for entry 7 were determined as optimal for the aminofluorination reaction.

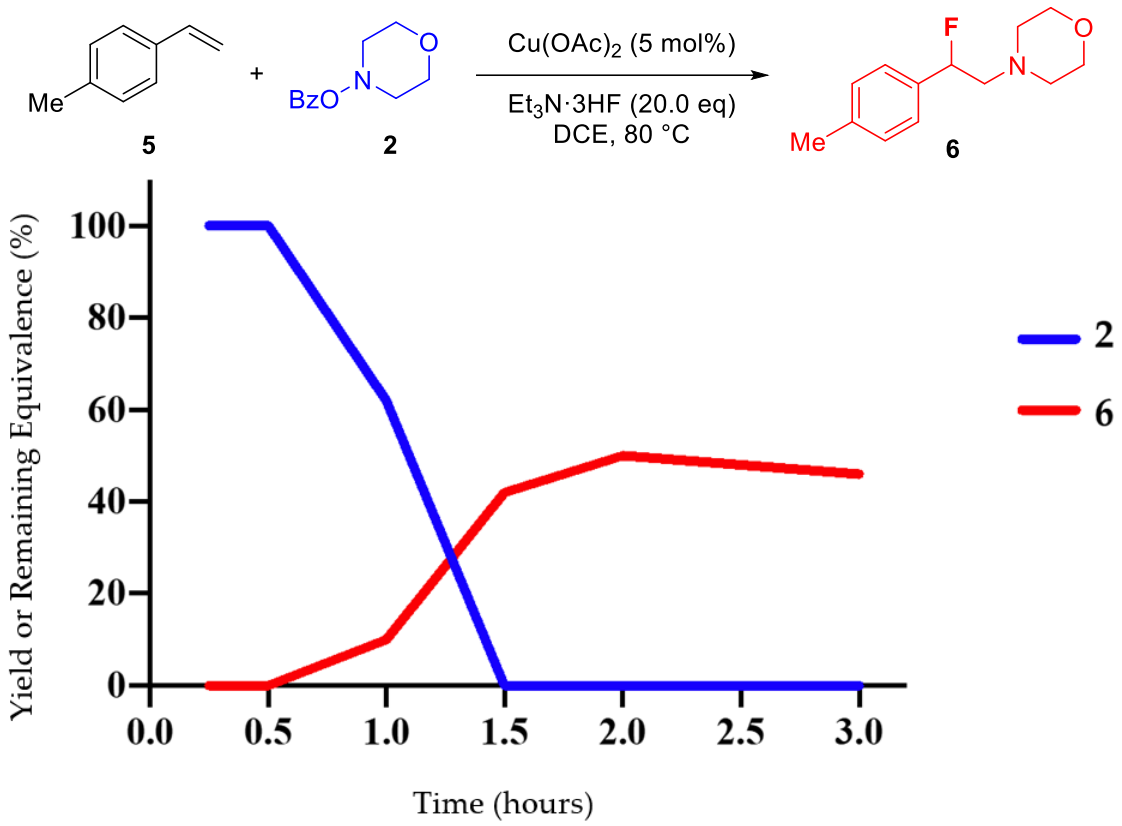


Figure 2: Time of completion for alkene aminofluorination reaction.

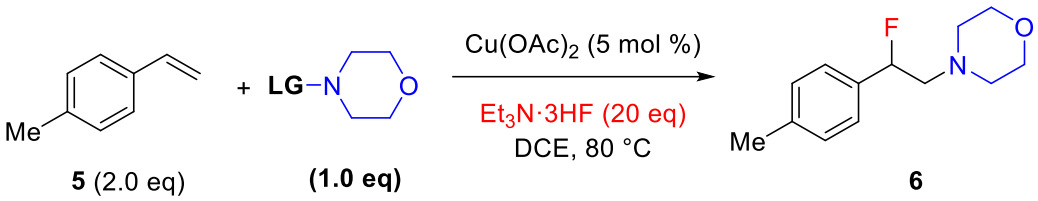
To determine how long the transformation took to complete, seven reactions with 4-methylstyrene 5 (0.2 mmol scale) were subjected to the established protocol. At 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 hours, one of the reactions was prematurely cooled and quenched. Conversion of starting materials to product, determined by NMR spectroscopy using CH_2Br_2 as a quantitative internal standard, was used to generate the above graph, which indicates complete hydroxylamine consumption occurs within 1.5 hours and product formation completes within 2.0 hours. These results reinforce the initial assumption that the reaction completes at the same time the hydroxylamine is completely consumed.

2.2.2 Exploration of the Effects of the Leaving Group

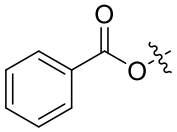
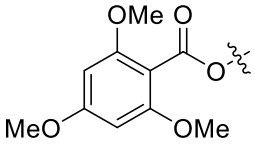
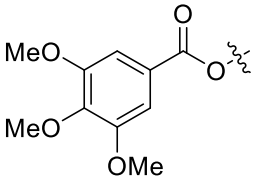
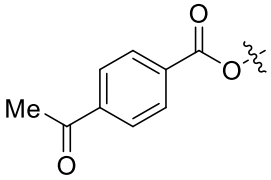
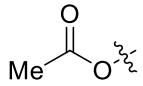
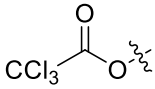
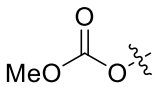
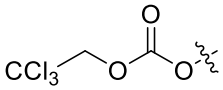
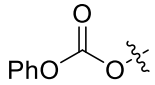
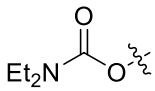
After the extensive optimization attempts previously outlined, we were discouraged that the yield was unable to improve. A possible reason could have been that the leaving group of the amino precursor plays a vital role in the efficacy of the transformation. Taking inspiration from Buchwald's discovery of a free energy relationship between aryl-substituted *O*-benzoyl-*N*,*N*-dialkylhydroxylamines and the rate of alkene hydroamination,[35] we endeavored to determine if the nature of the leaving group played a crucial part in the alkene aminofluorination transformation.

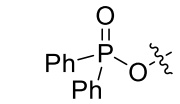
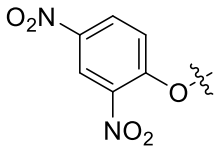
To determine the effect of the leaving group of the nitrogen precursor, various *O*-substituted *N*-hydroxylmorpholine reagents were prepared and tested against 4-methylstyrene (5) under the standard reaction conditions (Table 9). The electronic effect of the benzoate leaving group was evaluated through the use of electron-rich trimethoxybenzoate- and electron-deficient 4-acetylbenzoate- hydroxylamines 7, 8 and 9. Lack of any notable difference between these hydroxylamines suggest the electronics of benzoate leaving groups have no effect on the aminofluorination reaction. Hydroxylamine 10, containing an acetoxy leaving group, proved to react slightly faster than the analogous benzoates, but otherwise exhibited no advantage to the desired transformation. The electron-deficient hydroxylamine 11 degraded rapidly. Hydroxylamines bearing a carbonate leaving group were also capable of participating in the desired reaction, but displayed an overall reduced yield of the

Table 9: Screening of leaving group.



5 (2.0 eq) **(1.0 eq)** **6**

entry	LG		time (hours)	Yield (%)[a] **6**
1		**2**	2	48
2		**7**	2	47
3		**8**	2	48
4		**9**	2	48
5		**10**	1	41
6		**11**	0.25	6
7		**12**	8	19
8		**13**	2	19
9		**14**	5	19
10		**15**	6	38

11		**16**	>48	0
12		**17**	8	18

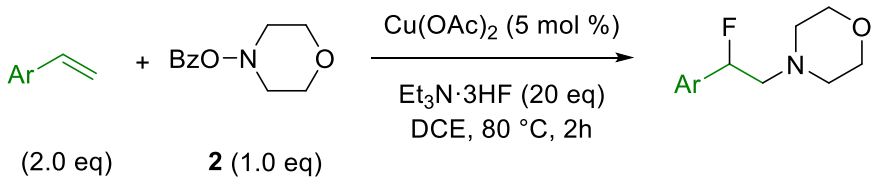
[a]Isolation yield.

desired product. It's notable that the tested carbonates displayed a variable rate of reactivity with the most electron-deficient hydroxylamine 13 taking only 2 hours to be completely consumed, and the electron-rich hydroxylamine 12 taking four times longer. This can be explained by the slowed rate of N–O bond cleavage in hydroxylamines in which the oxygen has less resonance away from the shared bond. In addition to carbonate leaving groups, hydroxylamine 15, which bears a carbamate leaving group, and *O*-aryl hydroxylamine 17 were both shown able to participate in the desired transformation. This nicely illustrates that copper-catalyzed N–O bond cleavage is not specific to *O*-acyl hydroxylamines, but may be extended to various underexplored reagents. Lastly, hydroxylamine 16, which carries a phosphinate leaving group, showed remarkable stability in the reaction and was unable to be consumed even after an extended period. Unfortunately, no prepared hydroxylamine proved to be more effective in the aminofluorination reaction than the simple *O*-benzoyl-*N*-hydroxylmorpholine 2.

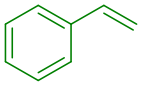
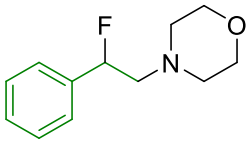
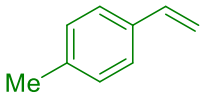
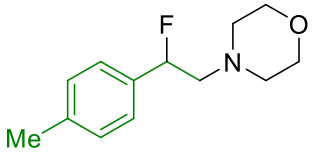
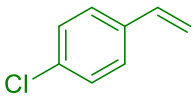
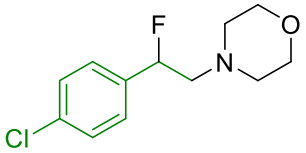
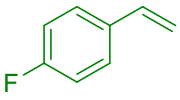
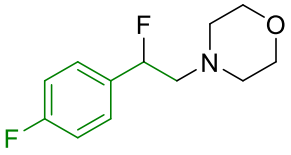
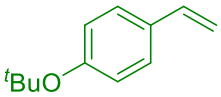
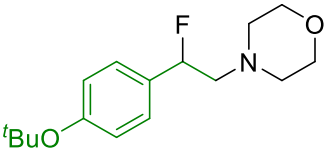
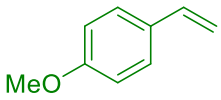
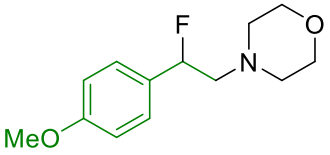
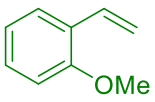
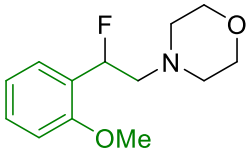
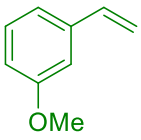
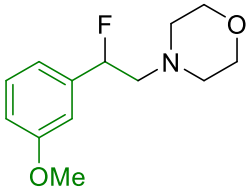
2.2.3 Discovery of Alkene Scope

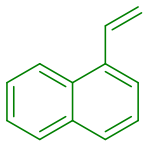
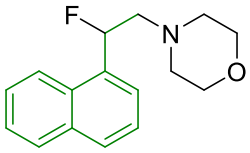
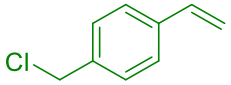
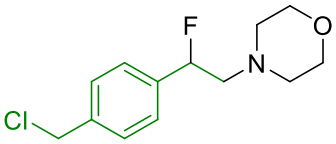
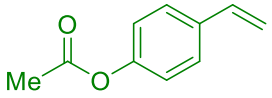
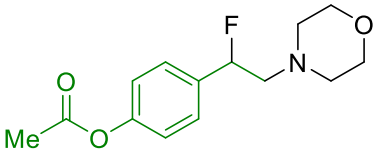
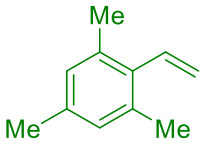
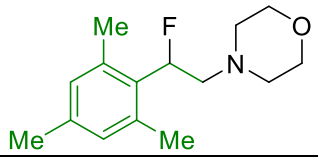
With a working procedure in hand for the *N*-alkylaminofluorination of alkenes, the limitations of the transformation were further investigated through the discovery of the substrate scope. Various styrenes were first subjected to the aminofluorination conditions to synthesize their corresponding β-fluoroamines (Table 10). Simple styrene 1 produced the desired product in a slight decrease compared to the 4-methylstyrene 5. This may indicate a slight stabilization of an electron deficient intermediate through induction. Styrenes bearing either a chlorine 18 or fluorine halogen 20 were well tolerated to produce the desired product in similar yield to styrene. Electron donating groups such as 4-OtBu and 4-OMe (22, 24) were also tolerated in the reaction condition, but did not improve yield as one would suspect based upon the results of 4-methylstyrene. Strongly donating groups may stabilize a benzylic carbocation and enable unproductive pathways, decreasing the overall yield. Between p- o- and m-substituted vinylanisoles 24, 26, and 28, ortho gave the highest yield while meta and para gave similar. Vinylnapthalene 30 also effectively produces the desired compound, illustrating extended conjugation does not negatively impact the reaction. Styrenes containing sensitive functionalities such as an alkyl halide (32) or acetoxy (34) are suitable reaction partners for the transformation. Sterically encumbered styrene 36 exhibits a decrease in yield, but is otherwise smoothly transformed.

Table 10: Styrene scope for aminofluorination reaction.



(2.0 eq) **2** (1.0 eq)

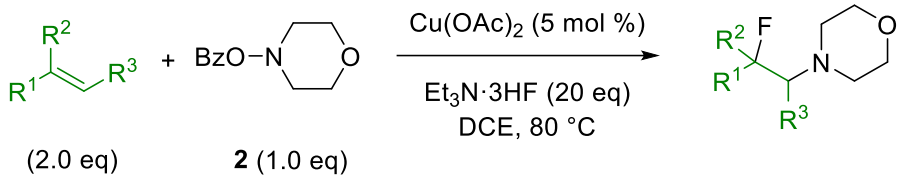
entry	alkene		product		Yield (%)[a]
1		**1**		**3**	38
2		**5**		**6**	49
3		**18**		**19**	32
4		**20**		**21**	33
5		**22**		**23**	30
6		**24**		**25**	25
7		**26**		**27**	38
8		**28**		**29**	25

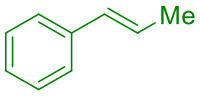
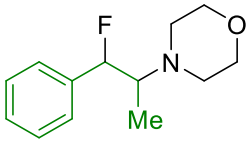
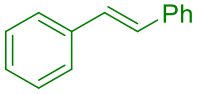
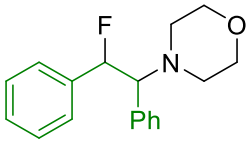
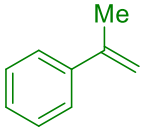
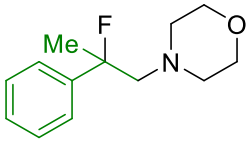
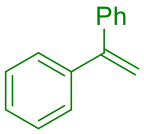
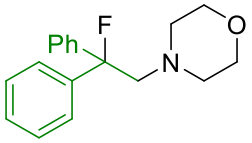
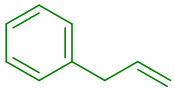
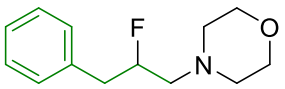
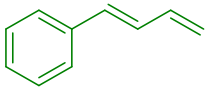
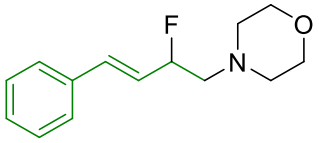
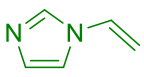
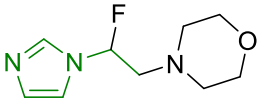
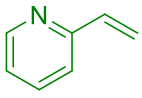
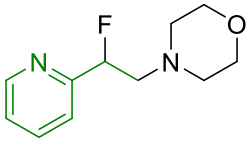
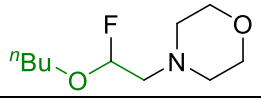
9		**30**		**31**	20
10		**32**		**33**	29
11		**34**		**35**	13
12		**36**		**37**	15

[a]Isolation yield.

Substituted styrenes 38, 40, 42, and 44 illustrated the ineffectiveness of the procedure in functionalizing disubstituted alkenes (Table 11). Of the disubstituted alkenes tested, trans-β-methylstyrene 38 was solely tolerated and produced a 1:1 diastereomeric mixture of products, which supports a reaction pathway that does not exclusively involve an S_N2 aziridinium ring opening. Unconjugated allyl benzene 46 produced a trace amount of product with good regioselectivity (determined from the crude ^{19}F NMR), demonstrating the necessity of benzylic stabilization. The diene 48 reacted to produce the 1,2-addition product in 9%. The 1,4-addition product was detected in trace (<5%) amounts, but was otherwise incapable of being isolated. Vinyl heterocycles and vinyl ether 50, 52, and 54 failed to react to generate the desired product.

Table 11: Disubstituted and non-styrenyl scope for alkene aminofluorination.



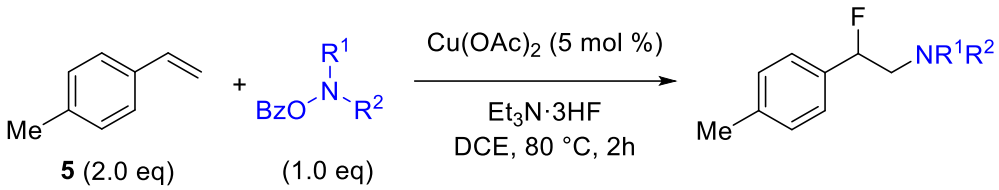
entry	alkene		product		Yield (%)[a]
1		**38**		**39**	35, 1:1 dr[b]
2		**40**		**41**	trace
3		**42**		**43**	trace
4		**44**		**45**	trace
5		**46**		**47**	(<5)[c]
6		**48**		**49**	9
7		**50**		**51**	ND
8		**52**		**53**	ND
9		**54**		**55**	ND

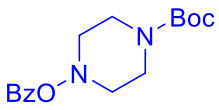
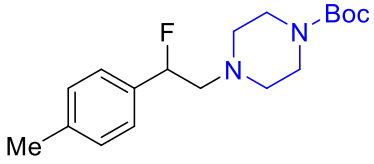
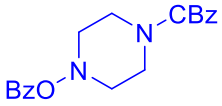
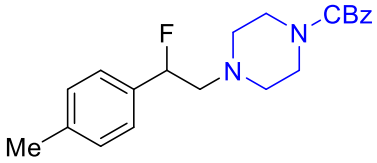
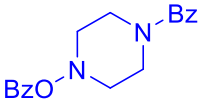
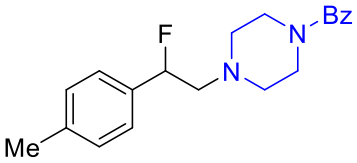
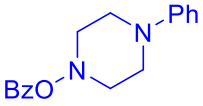
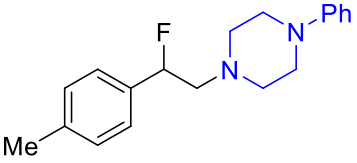
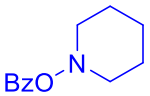
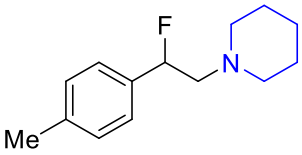
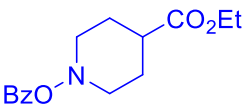
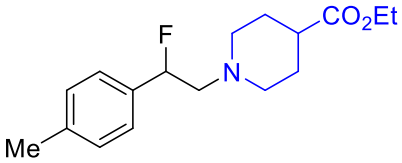
[a]Isolation yield. [b]Determined through ^{1}H NMR of unpurified mixture. [c]Yield determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard.

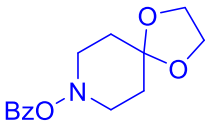
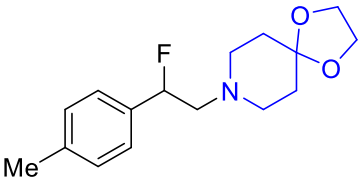
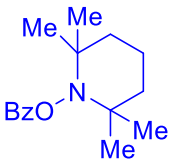
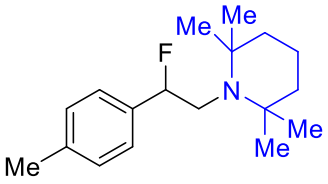
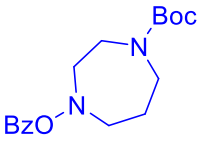
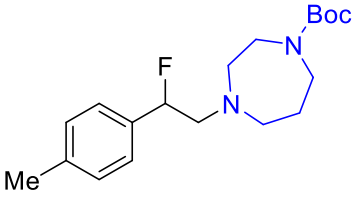
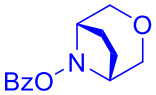
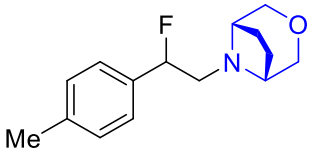
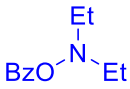
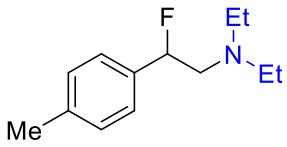
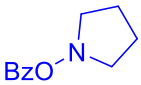
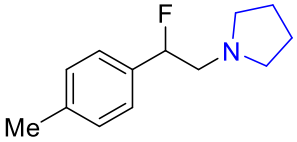
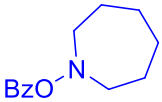
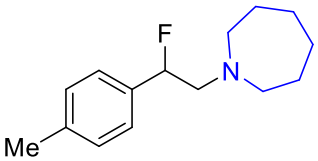
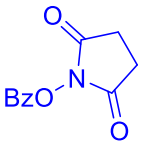
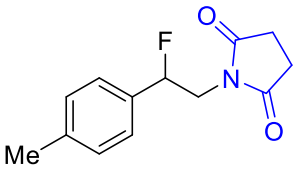
2.2.4 Discovery of Amine Scope

Next, the amine scope was probed with various *O*-benzoylhydroxylamines (Table 12). Most *N*-protected piperazine (56, 58, 60, and 62) precursors reacted smoothly under the standard reaction conditions. However, the reaction showed intolerance to the aniline moiety, a possible reason for the lack of reactivity of phenyl protected piperazine hydroxylamine 62. Piperidine precursors 64 showcased almost no reactivity, but when an electron withdrawing group was attached (66 and 68) yields returned to isolable amounts. Interestingly, when the α-protons of the piperidine precursor are replaced with methyl substituents (70), the yield also increases. This may be due to a degradation pathway of the amino precursor in which an α-proton is lost to generate an imine.[36] Homopiperazine hydroxylamine 72 proved that the reaction is not specific to 6-membered rings and can be extended to cyclic amines of other ring sizes. Morpholine hydroxylamine 74 revealed bridged amine precursors are capable of undergoing the reaction as well. Unfortunately, acyclic hydroxylamines, such as 76 failed to produce any isolable amount of the desired product. Pyrrolidine and azepane precursors 78 and 80 showed slightly less reactivity than the analogous 6-membered piperidine, while succinimide precursor 82 did not participate in the desired reaction pathway to any degree. The transformation is thus uniquely suited to cyclic amine precursors bearing an electron-withdrawing moiety.

Table 12: Amine scope for alkene aminofluorination.



entry	alkene		product		Yield (%)[a]
1		**56**		**57**	33
2		**58**		**59**	37
3		**60**		**61**	44
4		**62**		**63**	trace
5		**64**		**65**	(5)[b]
6		**66**		**67**	18

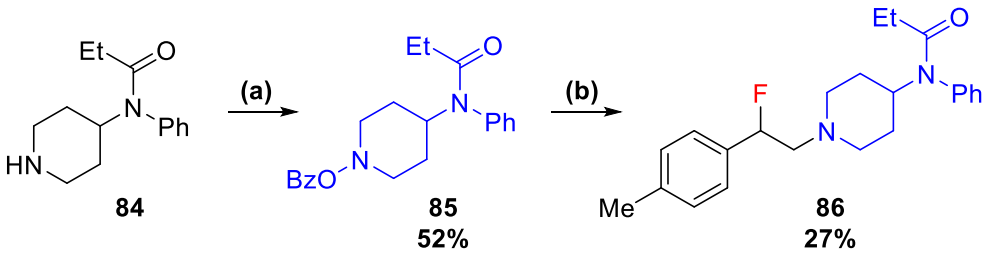
7		**68**		**69**	21
8		**70**		**71**	14
9		**72**		**73**	22
10		**74**		**75**	41
11		**76**		**77**	trace
12		**78**		**79**	trace
13		**80**		**81**	trace
14		**82**		**83**	ND

[a]Isolation yield. [b]Yield determined by ^{19}F NMR spectroscopy with 1,2,4,5-tetrafluorobenzene as a quantitative internal standard.

2.2.5 Demonstration of Applicability

To demonstrate the synthetic utility of the described method, β-fluorinated fentanyl analogue 86 was prepared (Scheme 14). The commercially available *N,N*-dialkylamine norfentanyl (84) was first oxidized to the *O*-benzoylhydroxylamine 85 following the procedure established by Ganem.[30] The fentanyl analogue was then synthesized via the established three-component aminofluorination with 4-methylstyrene and $Et_3N•3HF$. Although the yield of the transformation is modest, the expediency in which the fluorinated analogue was prepared illustrates the great advantage of this synthetic method.

Scheme 14: Synthesis of fluorinated fentanyl analogue.

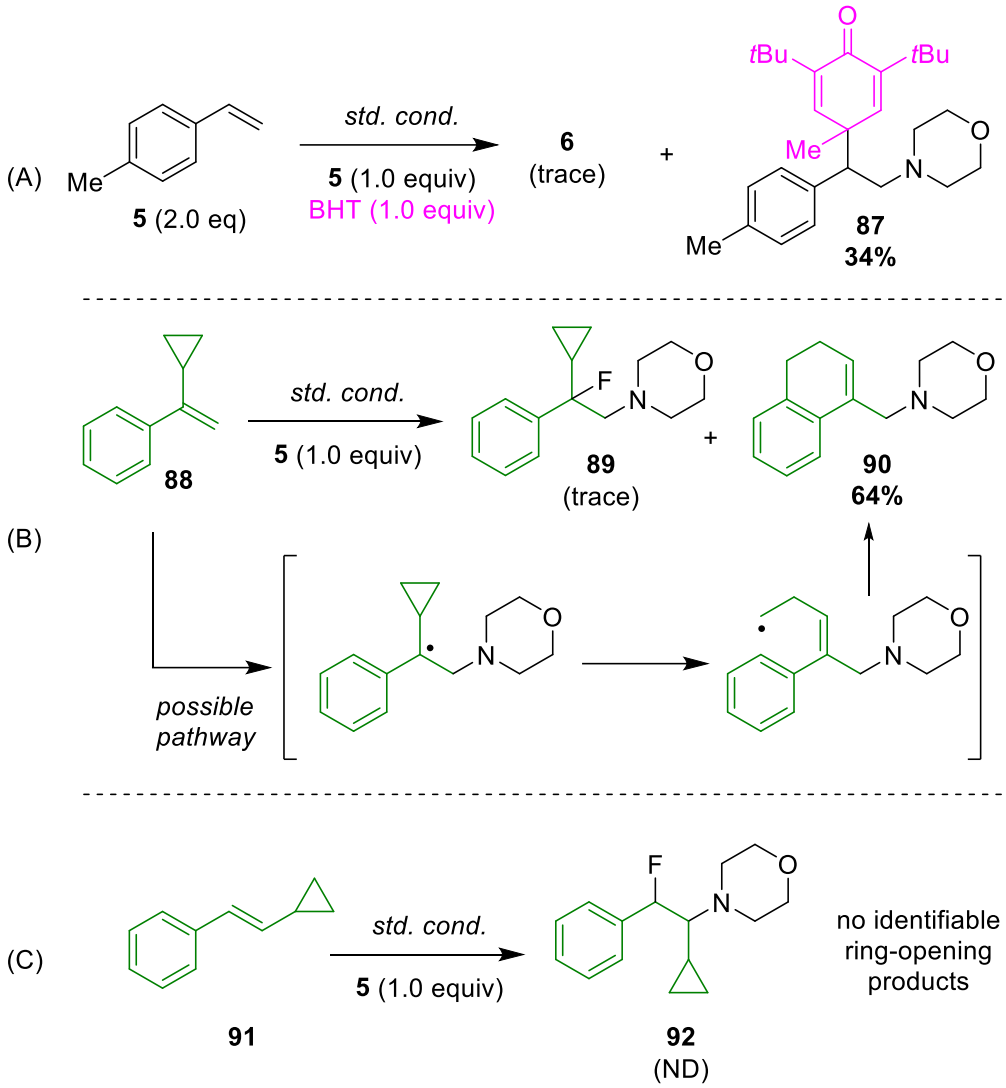


(a) norfentanyl **84** (1.7 mmol, 1.1 equiv), BPO (1.5 mmol, 1.0 equiv), Na_2HPO_4, (2.3 mmol, 1.5 equiv), DMF (10 mL), rt, 4 h. (b) **85** (0.2 mmol, 1.0 equiv), 4-methylstyrene (0.4 mmol, 2.0 equiv), $Cu(OAc)_2$ (1.82 mg, 5.0 mol %), $Et_3N•3HF$ (652 μL, 20.0 equiv), DCE (1.0 mL), 80 °C, 2.5 h, in 10-mL sealed FEP Tube.

2.2.6 Mechanistic Studies

To gain insight on the mechanism of the transformation, radical trapping experiments were carried out (Scheme 15). Butylated hydroxytoluene (BHT), a common radical trap, was added to a standard reaction of 4-methylstyrene and *O*-benzoylhydroxylamine. Instead of the expected β-fluoroamine product 6, BHT

Scheme 15: Radical trapping experiments for alkene aminofluorination reaction.



adduct 87 was observed and isolated. This strongly suggests that the transformation proceeds through an amine-initiation, and an intermediate of the reaction contains the benzylic stabilized carbon-centered radical. To further probe this hypothesis, cyclopropylstyrenes 88 and 91 were subjected to the reaction condition. While no ring opening products were observed from 91, α-cyclopropylstyrene 88 produced the ring

opening product 90 in relatively high yield, which further implicates a radical pathway is present.

Based on these results, one reasonable reaction pathway begins with the copper-catalyzed reductive N–O bond cleavage to generate a nitrogen-centered radical which can add to the alkene and generate a stabilized carbon-centered radical in a regioselective manner. Further studies are underway to elucidate the nature of the C–F bond-forming step, but the relatively high yield of 90 suggests that C–F bond formation is rate-limiting.

3. Conclusion

In conclusion, a novel method for the preparation of β-fluorophenethyl-*N*,*N*-dialkylamines has been disclosed. The transformation proceeds from a variety of *O*-protected-*N*,*N*-dialkylhydroxylamines and can effectively convert aryl-substituted olefins to value-added chemicals with beneficial pharmacological parameters. The utility of the method was demonstrated through the synthesis of a β-fluoro fentanyl analogue, and mechanistic insight was gained through radical trapping experiments which support an amine-initiated pathway.

4. Supporting Information

4.1 General Methods and Procedures

General procedures for starting material syntheses

Round-bottom flasks and stir bars were dried either with a propane torch or in an oven at 140 °C overnight and cooled/stored in a desiccator filled with Drierite. Optimization and substrate screens were performed in 10-mL FEP Tubes without prior drying, and a Teflon-coated micro stir bar. All other reactions were performed in round-bottom flasks with rubber septa and Teflon-coated stir bars. Plastic syringes were used for the transfer of pure solvents, while glass pipets were used for transfer of crude reaction mixtures. Analytical thin-layer chromatography (TLC) was performed using aluminum plates coated with a 0.25 mm layer of 230–400 mesh silica gel with fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and treatment with mainly vanillin or rarely KMnO4 stain. Organic solutions were concentrated under reduced pressure using a rotary evaporator and flash chromatography performed using 60 Å silica gel and HPLC-grade solvents.

Materials

Commercial reagents and anhydrous solvents were used as received. Specific anhydrous solvents (Et_2O, CH_2Cl_2, Toluene, Dioxane, and THF) were obtained from an Innovative Technologies solvent purification system. Commercially available substrates were purchased in >95% purity and used without further purification.

Instrumentation

Nuclear magnetic resonance spectra were recorded on either a Varian 400 MHz spectrophotometer or Bruker 500 MHz spectrophotometer at room temperature. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm, δ) and referenced to residual protium in $CDCl_3$ (δ 7.26). NMR values are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm^{-1}) with selected peaks shown. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer.

General procedures for optimization screening

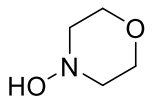
To a 10-mL FEP tube with Teflon-coated micro stir bar was added *O*-benzoylhydroxylamine and copper catalyst. Solvent (1.0 mL), styrene, and fluorinating reagent were sequentially added via syringe. The mixture was then stirred and heated until the consumption of *O*-benzoylhydroxylamine, verified by TLC analysis. The resulting reaction mixture was cooled to room temperature and quenched through the addition of Et_3N (0.5 mL). The solution was then diluted with ethyl acetate to a final volume of 5.0 mL and filtered through a plug of activated, neutral Al_2O_3 (Brockman grade I, 58–60Å). The filtrate was concentrated under reduced pressure, providing the crude reaction mixture. The crude reaction mixture was either purified by

silica column chromatography and added to CH_2Br_2 (0.1 mmol) and 1,2,4,5-tetrafluorobenzene (0.05 mmol) as quantitative internal standards in $CDCl_3$ (0.4 mL) and analyzed by NMR spectrometry.

4.2 Synthesis and Characterization Data for Starting Materials

*General procedure for the preparation of hydroxylamine starting materials (**GP2**):*

To a 15-mL round-bottom flask was added morpholin-4-ol (433 mg, 4.2 mmol, 1.05 equiv), dimethylaminopyridine (9.0 mg, 0.075 mmol, 0.019 equiv), freshly distilled CH_2Cl_2 (2 mL), and triethylamine (0.59 mL, 4.2 mmol, 1.05 equiv). The temperature was reduced to 0 °C and the acyl chloride (4.0 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added. The reaction was allowed to react at room temperature for 30 minutes, until the consumption of acyl chloride monitored by TLC. The reaction mixture was then washed with aqueous HCl (1 M, 5 mL x2). The separated organic layer was dried over Na_2SO_4 and the filtrate concentrated in vacuo. Purification by column chromatography (5% MeOH, 30% ethyl acetate, 65% hexanes unless otherwise noted) generated the desired product.

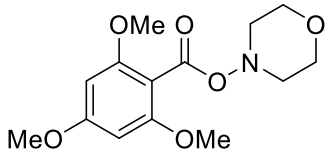


Morpholin-4-ol

To a 250-mL round-bottom flask was added NaOMe (1.59 g, 28 mmol, 1.4 equiv) and MeOH (70 mL). In a separate 100-mL round-bottom flask was added *O*-benzoyl-*N*-

hydroxylmorpholine (4.14 g, 20 mmol, 1.0 equiv) and Et_2O (60 mL). The dissolved hydroxylamine ester was then added to the NaOMe solution via syringe. The mixture was allowed to stir for 12 hours, then directly dried in vacuo. The crude mixture was purified by flash column chromatography (30% ethyl acetate-hexanes → 40% ethyl acetate-hexanes) to afford **morpholin-4-ol** as a colorless oil (1.33 g, 69%). Spectroscopic data match the commercially available *N*-hydroxylamine (CAS 5765-63-9).

^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (br, 1H), 3.91 (d, *J* = 12.0 Hz, 2H), 3.76–3.47 (m, 2H), 3.14 (d, *J* = 11.0 Hz, 2H), 2.72 (td, *J* = 11.0, 3.2 Hz, 2H).

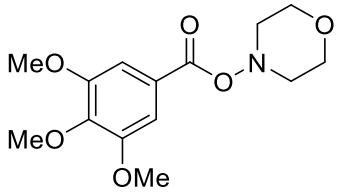


7

Morpholino 2,4,6-trimethoxybenzoate

To a 100-mL round-bottom flask was added 2,4,6-trimethoxybenzoic acid (0.849 g, 4.0 mmol, 1.0 equiv), CH_2Cl_2 (10 mL), oxalyl chloride (406 μL, 4.8 mmol, 1.2 equiv), and dimethylformamide (0.2 mL). Upon the discontinuation of gas evolution, the mixture was directly concentrated under reduced pressure. The mixture was next diluted with CH_2Cl_2 (10 mL), and morpholin-4-ol (433 mg, 4.2 mmol, 1.05 equiv) was added over 5 minutes, followed by the addition of triethylamine (585 μL, 4.2 mmol, 1.05 equiv). Upon consumption of acid starting material monitored by TLC, the reaction was quenched through the addition of saturated aqueous NH_4Cl (10 mL) and H_2O (20 mL). The layers were separated, and organic washed with saturated aqueous NH_4Cl (10 mL x3),

saturated aqueous $NaHCO_3$ (10 mL x3), H_2O (10 mL x3), and brine (10 mL x2). The organic layer was then dried over Na_2SO_4, and the filtrate concentrated in vacuo. Purification by flash column chromatography (20% % ethyl acetate- hexanes → 60% ethyl acetate-hexanes) gave **7** as a white solid (493 mg, 42%) R_f = 0.33 (10% MeOH, 40% ethyl acetate, 50% hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 2H), 3.98–3.75 (m, 13H), 3.44 (d, *J* = 9.3 Hz, 2H), 3.04–2.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.54, 162.91, 158.88, 104.26, 90.60, 65.80, 56.77, 55.91, 55.44. FTIR (thin film): cm^{-1} 2965, 2845, 1748, 1607, 1590, 1458, 1243, 1228, 1129, 1039. HRMS-ESI (m/z): Calculated for ($C_{14}H_{20}NO_6$) ($[M+H]^+$): 298.1285; found: 298.1287.

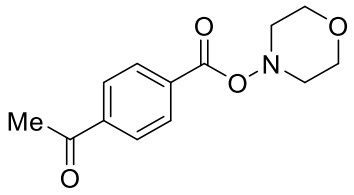


8

Morpholino 3,4,5-trimethoxybenzoate

To a 100-mL round-bottom flask was added 3,4,5-trimethoxybenzoic acid (1.02 g, 4.8 mmol, 1.2 equiv), CH_2Cl_2 (15 mL), and 1,1'-carbonyldiimidazole (778 mg, 4.8 mmol, 1.2 equiv). The mixture was allowed to stir overnight, until the formation of CO_2 gas halted. Morpholin-4-ol (413 mg, 4.0 mmol, 1.0 equiv) was next added in 5 mL CH_2Cl_2. The mixture was allowed to stir until the consumption of hydroxylamine monitored by TLC. The solvent was removed directly in vacuo, then the crude mixture was diluted with ethyl acetate (10 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL

x2), saturated aqueous NH_4Cl (10 mL x3), brine (10 mL x2), dried over Na_2SO4, filtered, and concentrated in vacuo to afford the crude product. Purification by flash column chromatography (40% ethyl acetate-hexanes → 50% ethyl acetate-hexanes) gave **8** as a white solid (716 mg, 60%). Spectroscopic data matched the reported literature.[37] ^1H NMR (400 MHz, CDCl3) δ 7.25 (s, 2H), 4.02–3.78 (m, 13H), 3.52–3.39 (m, 2H), 3.11–2.96 (m, 2H).

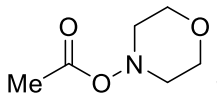


9

Morpholino 4-acetylbenzoate

To a 100-mL round-bottom flask was added 4-acetylbenzoic acid (0.657 g, 4.0 mmol, 1.0 equiv), CH_2Cl_2 (10 mL), oxalyl chloride (406 μL, 4.8 mmol, 1.2 equiv), and dimethylformamide (0.2 mL). Upon the discontinuation of gas evolution, the mixture was directly concentrated under reduced pressure. The mixture was next diluted with CH_2Cl_2 (10 mL), and morpholin-4-ol (433 mg, 4.2 mmol, 1.05 equiv) was added over 5 minutes, followed by the addition of triethylamine (585 μL, 4.2 mmol, 1.05 equiv). Upon consumption of acid starting material monitored by TLC, the reaction was quenched through the addition of saturated aqueous NH_4Cl (10 mL) and H_2O (20 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (10 mL x3), saturated aqueous $NaHCO_3$ (10 mL x3), H_2O (10 mL x3), and brine (10 mL x2), then dried over Na_2SO_4. The filtrate was concentrated in vacuo. Purification by flash column

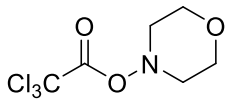
chromatography (10% ethyl acetate- hexanes → 30% ethyl acetate-hexanes) gave **9** as a white solid (545 mg, 55%). R_f = 0.18 (30% ethyl acetate-hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 4.08–3.72 (m, 4H), 3.57–3.34 (m, 2H), 3.14–2.90 (m, 2H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.32, 163.69, 140.36, 132.85, 129.65, 128.19, 65.79, 56.99, 26.82. FTIR (thin film): cm^{-1} 2967, 2900, 2858, 1737, 1685, 1404, 1240, 1100, 1083, 857, 763. HRMS-ESI (m/z): Calculated for ($C_{13}H_{16}NO_4$) ($[M+H]^+$): 250.1074; found: 250.1077.



10

Morpholino acetate

Preparation via **10** gave **2ae** as a light-yellow oil (375 mg, 65%). R_f = 0.34 (50% Ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.85 (d, *J* = 10.9 Hz, 2H), 3.77–3.65 (br. m, 2H), 3.23 (d, *J* = 9.6 Hz, 2H), 2.87–2.76 (br. m, 2H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.78, 65.62, 56.66, 19.52. FTIR (thin film): cm^{-1} 1756, 1210, 1102, 1003, 891, 857. HRMS-ESI (m/z): Calculated for ($C_6H_{11}NO_3Na$) ($[M+Na]^+$): 168.0631; found: 168.0628.

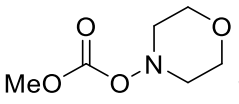


11

Morpholino 2,2,2-trichloroacetate

Preparation via **GP2** and purification by column chromatography (20% ethyl acetate-hexenes) gave **11** as a yellow solid (726 mg, 73%). R_f = 0.34 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.97 (d, *J* = 11.9 Hz, 2H), 3.82–3.72 (br. m, 2H), 3.43 (d, *J* =

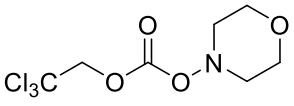
9.9 Hz, 2H), 3.11–3.01 (br. m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.04, 88.88, 65.58, 56.84. FTIR (thin film): cm^{-1} 1777, 1460, 1267, 1194, 1098, 962, 865, 812, 674. HRMS-ESI (m/z): Calculated for ($C_6H_9{}^{35}Cl_3NO_3$) ([M+H]$^+$): 247.9643; found: 247.9643.



12

Methyl morpholino carbonate

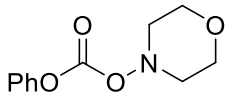
Preparation via **GP2** gave **12** as a light-yellow oil (496 mg, 77%). R_f = 0.48 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.91 (d, *J* = 11.3 Hz, 2H), 3.80 (s, 3H), 3.77–3.70 (br. m, 2H), 3.34 (d, *J* = 9.7 Hz, 2H), 3.00–2.85 (br. m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.81, 65.63, 56.83, 54.97. FTIR (thin film): cm^{-1} 1767, 1440, 1268, 1229, 1100, 1052, 860. HRMS-ESI (m/z): Calculated for ($C_6H_{12}NO_4$) ([M+H]$^+$): 162.0761; found: 162.0761.



13

Morpholino (2,2,2-trichloroethyl) carbonate

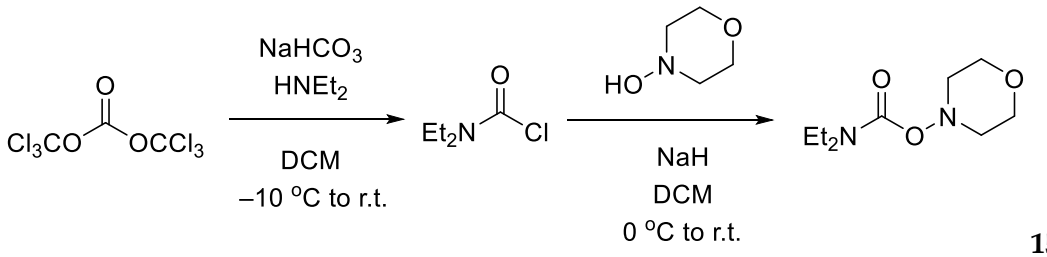
Preparation via **GP2** gave **13** as a light-yellow oil (1.068g, 96%). R_f = 0.62 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.78 (s, 2H), 3.94 (d, *J* = 11.7 Hz, 2H), 3.79–3.71 (br. m, 2H), 3.40 (d, *J* = 9.8 Hz, 2H), 3.03–2.96 (br. m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.21, 94.19, 76.75, 65.74, 57.01. FTIR (thin film): cm^{-1} 1778, 1459, 1374, 1270, 1214, 1100, 1051, 802. HRMS-ESI (m/z): Calculated for ($C_7H_{11}{}^{35}Cl_3NO_4$) ([M+H]$^+$): 277.9748; found: 277.9748.



14

Morpholino phenyl carbonate

Preparation via **GP2** gave **14** as a white solid (862 mg, 97%). R_f = 0.59 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.35 (m, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 3.96 (d, *J* = 11.4 Hz, 2H), 3.83–3.71 (br. m, 2H), 3.45 (d, *J* = 9.6 Hz, 2H), 3.09–2.90 (br. m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 152.60, 150.81, 129.44, 126.07, 120.77, 65.70, 56.94. FTIR (thin film): cm^{-1} 1776, 1591, 1495, 1191, 1099, 1004, 798, 686. HRMS-ESI (m/z): Calculated for ($C_{11}H_{14}NO_4$) ([M+H]$^+$): 224.0917; found: 224.0919.



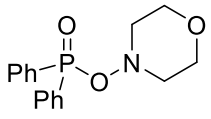
15

Morpholino diethylcarbamate

Diethylcarbamic chloride was synthesized following a previously reported method.[38] A solution of diethylamine (0.62 mL, 6.0 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise over 10 minutes to a stirred slurry of $NaHCO_3$ (1.01 g, 12.0 mmol, 3.0 equiv) and triphosgene (1.187 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL) at –10 °C. The reaction was allowed to warm to room temperature for 4 hours until the consumption of triphosgene. The mixture was then filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (5% ethyl acetate-hexanes) produced

diethylcarbamic chloride as a light-yellow oil (364 mg, 67 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 1.23 (t, J = 6.5 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 1H).

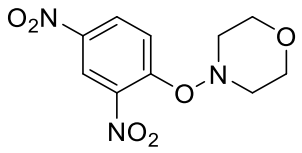
A solution of morpholin-4-ol (397 mg, 3.85 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (0.4 mL) was added dropwise over 5 minutes to a stirred slurry of NaH (169 mg, 4.24 mmol, 1.1 equiv) in freshly distilled CH_2Cl_2 (2 mL) under N_2. Diethylcarbamic chloride was next added via syringe over 8 minutes. The reaction was allowed to warm to room temperature for 45 minutes, until the consumption of morpholin-4-ol. The reaction mixture was diluted with 20 mL CH_2Cl_2 and washed with aqueous HCl (2 M, 8 mL) and brine (12 mL). The organic layer was dried over Na_2SO_4 and the filtrate concentrated in vacuo. Purification through a silica plug (5 mL) with 10% MeOH, 27% ethyl acetate, 63% hexanes to produced **15** as a yellow oil (0.74g, 93%). R_f = 0.14 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.88–3.79 (m, 2H), 3.78–3.69 (m, 2H), 3.36–3.26 (m, 2H), 3.24–3.12 (m, 4H), 2.92–2.60 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.59, 65.67, 56.96, 41.64, 13.59. FTIR (thin film): cm^{-1} 1713, 1414, 1260, 1155, 1101, 967, 864, 757. HRMS-ESI (m/z): Calculated for ($C_9H_{19}N_2O_3$) ($[M+H]^+$): 203.1390; found: 203.1394.



16

Morpholino diphenylphosphinate

16 was synthesized following a previously reported method with modification.[39] To a 10-mL round-bottom flask added morpholin-4-ol (412 mg, 4.0 mmol, 1.0 equiv), triethylamine (1.39 mL, 10 mmol, 2.5 equiv) and CH_2Cl_2 (0.5 mL). Temperature was reduced to 0 °C, then diphenylphosphinyl chloride (1.92 mL, 4.8 mmol, 1.2 equiv) was added. The reaction was allowed to react at room temperature, until the consumption of morpholin-4-ol. CH_2Cl_2 was then removed through rotary evaporator and the residue was stirred with diethyl ether (10 mL) and decanted four times. The combined extracts were filtered through a silica/celite pad and concentrated in vacuo to give **16** as a white solid (308 mg, 1.01 mmol, 25%). R_f = 0.13 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.55–7.50 (m, 2H), 7.47–7.41 (m, 4H), 3.82 (d, J = 11.8 Hz, 2H), 3.58–3.50 (br. m, 2H), 3.25 (d, J = 10.3 Hz, 2H), 3.04–2.96 (br. m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 132.18 (d, J_{C-P} = 2.7 Hz, 2C), 131.88 (d, J_{C-P} = 9.9 Hz, 4C), 130.67 (d, J_{C-P} = 135.3 Hz, 2C), 128.31 (d, J_{C-P} = 12.9 Hz, 4C), 65.81 (2C), 58.71 (d, J_{C-P} = 2.7 Hz, 2C). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 33.63–33.36 (m). FTIR (thin film): cm^{-1} 1438, 1227, 1128, 1020, 866, 787, 726, 693, 546, 530. HRMS-ESI (m/z): Calculated for ($C_{16}H_{19}NO_3P$) ($[M+H]^+$): 304.1097; found: 304.1092.

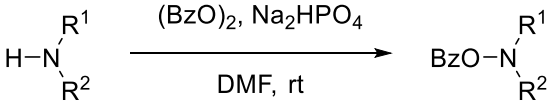


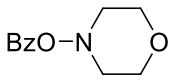
17

4-(2,4-Dinitrophenoxy)morpholine

Prepared following a previously reported method.[40] Spectroscopic data were in agreement. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.41 (d, *J* = 9.3 Hz, 1H), 7.90 (d, *J* = 9.3 Hz, 1H), 4.06 (d, *J* = 11.4 Hz, 2H), 3.75 (t, *J* = 11.4 Hz, 2H), 3.33 (d, *J* = 10.3 Hz, 2H), 3.16 (t, *J* = 10.3 Hz, 2H).

O-Benzoylhydroxylamines (**2**, **56**, **58**, **60**, **62**, **64**, **64**, **66**, **70**, **72**, **76**, **78**, and **80**) were synthesized according to the Ganem protocol.[30]





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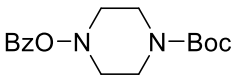

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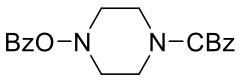

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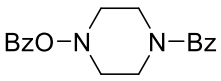

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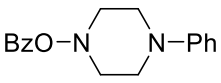

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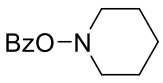

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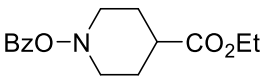

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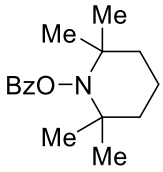

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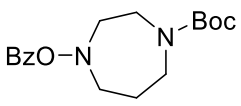

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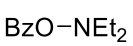

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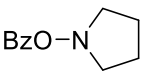

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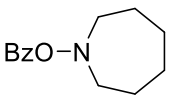

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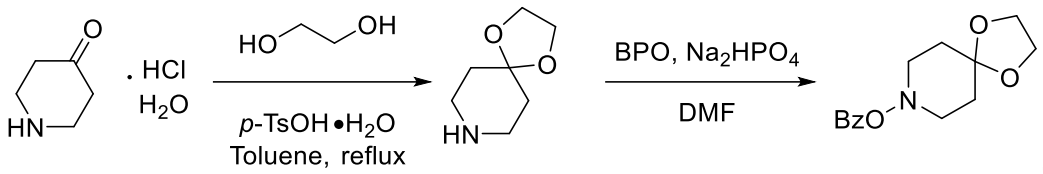
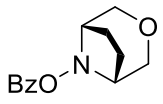


68

1,4-Dioxa-8-azaspiro[4.5]decan-8-yl benzoate

Prepared following a previously reported method[41] with modification. To a 25-mL round-bottom flask was added 4-piperidone monohydrate hydrochloride (768 mg, 5.0 mmol, 1.0 equiv), toluene (8.0 mL), ethylene glycol (0.28 mL, 5.0 mmol, 1.0 equiv), and *p*-toluenesulfonic acid monohydrate (95.1 mg, 0.5 mmol, 0.1 equiv). The reaction was heated to reflux in a Dean-Stark apparatus. The mixture was allowed to react for 15 hours, at which point no additional water was observed produced. The mixture was next cooled to room temperature and concentrated in vacuo. The resulting orange solid was dissolved with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL x 2). The separated aqueous layer was then extracted with a mixture of DCM/*i*-PrOH (1:1, 20 mL x 2). The organic layers were combined and dried over Na_2SO_4 and the filtrate concentrated in vacuo to give 1,4-dioxa-8-azaspiro[4.5]decane as a yellow oil, which was directly used for the next step. Preparation via the Ganem protocol and purification through flash column chromatography (100% hexanes → 30% ethyl acetate-hexanes) gave **68** as a colorless oil (329 mg, 33% over two steps). R_f = 0.21 (50% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45–7.39 (m, 2H), 3.98 (s, 4H), 3.43 (br. s, 2H), 3.25 (br. s, 2H), 1.95 (t, *J* = 5.7 Hz, 4H).

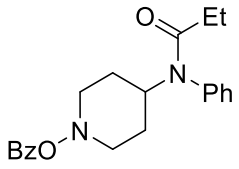
^{13}C NMR ($CDCl_3$, 126 MHz): δ 164.71, 133.02, 129.37, 129.33, 128.36, 105.97, 77.25, 77.00, 76.75, 64.46, 64.31, 53.92, 32.52. FTIR (thin film): cm^{-1} 1735, 1451, 1246, 1083, 1064, 709. HRMS-ESI (m/z): Calculated for ($C_{14}H_{18}NO_4$) ([M+H]$^+$): 264.1230; found: 264.1235.



74

3-Oxa-8-azabicyclo[3.2.1]octan-8-yl benzoate

Preparation via the Ganem protocol[30] gave **74** as an off-white solid (550 mg, 40%). R_f = 0.48 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 8.4, 1.4 Hz, 2H), 7.56 (tt, *J* = 7.1, 1.4 Hz, 1H), 7.45–7.40 (m, 2H), 4.00 (d, *J* = 11.5 Hz, 2H), 3.79 (d, *J* = 4.0 Hz, 2H), 3.66 (dd, *J* = 11.5, 2.7 Hz, 2H), 2.19–2.02 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.61, 133.02, 129.48, 129.27, 128.41, 72.38, 66.16, 25.95. FTIR (thin film): cm^{-1} 2954, 2863, 1733, 1249, 1080, 1063, 708. HRMS-ESI (m/z): Calculated for ($C_{13}H_{16}NO_3$) ([M+H]$^+$): 234.1125; found: 234.1129.

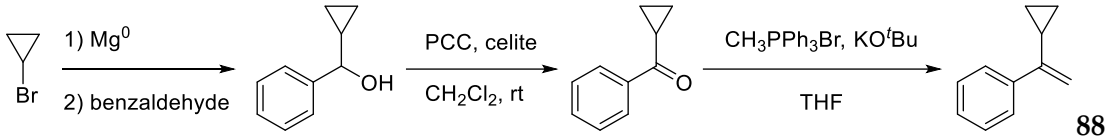


8**5**

4-(*N*-Phenylpropionamido)piperidin-1-yl benzoate

Preparation via the Ganem protocol[30] gave 8**5** as a white solid (284 mg, 52%). R_f = 0.23 (30% ethyl acetate-hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.48–7.33 (m, 5H), 7.07 (d, *J* = 6.6 Hz, 2H), 4.80 (t, *J* = 11.9 Hz, 1H), 3.52 (d, *J* = 9.1 Hz, 2H), 2.91 (t, *J* = 10.7 Hz, 2H), 2.01–1.85 (m, 2H), 1.93 (q, *J* = 7.4 Hz, 2H), 1.74 (q, *J*

= 11.9 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.74, 164.66, 138.34, 133.02, 130.34, 129.43, 129.38, 129.21, 128.53, 128.33, 56.09, 50.68, 29.37, 28.44, 9.55. FTIR (thin film): cm^{-1} 3061, 2937, 1737, 1653, 1244, 707. HRMS-ESI (m/z): Calculated for ($C_{21}H_{25}N_2O_3$) ([M+H]$^+$): 353.1860; found: 353.1869.

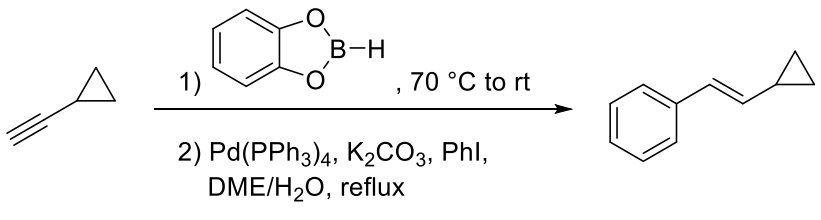


88

(1-Cyclopropylvinyl)benzene

Prepared following a previously reported method[42] with modifications. Magnesium turnings (220 mg, 9.15 mmol, 1.83 equiv) and an iodine spike were added to a 50-mL flame-dried two-necked round-bottom flask and vacuum purged and backfilled with N_2 x3. Freshly distilled THF (8.35 mL) was added, followed by dropwise addition of cyclopropyl bromide solution (0.67 mL, 8.35 mmol, 1.67 equiv in 4.2 mL THF). The solution was stirred at room temperature for 4 hours. To a separate flame-dried 100-mL round-bottom flask purged three times (backfilling with N_2) was added freshly distilled THF (10 mL) and 2-bromobenzaldehyde (0.51 mL, 5.0 mmol, 1.0 equiv). The solution was cooled to 0 ˚C, and cyclopropylmagnesium bromide solution was added slowly. The solution was allowed to stir at room temperature for 16 hours. The reaction was then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was the extracted with ethyl acetate (10mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the filtrate concentrated in vacuo. Purification by flash

column chromatography (5% ethyl acetate-hexanes) gave cyclopropyl(phenyl)methanol as a colorless oil (0.40 g, 54%). An anhydrous solution of cyclopropyl(phenyl)methanol (0.40 g, 2.7 mmol, 1.0 equiv) in CH_2Cl_2 (3.1 mL) was added dropwise over 15 minutes to an anhydrous suspension of pyridinium chlorochromate (1.17 g, 5.41 mmol, 2.0 equiv) and celite (1.16 g) in CH_2Cl_2 (16.6 mL). The reaction was allowed to stir for 3.5 h at room temperature, then quenched with CH_2Cl_2 (10 mL) and filtered through a pad of silica. Purification by column chromatography (100% hexanes → 5% ethyl acetate-hexanes) produced cyclopropyl(phenyl)methanone as a clear oil (350 mg, 89%). To a 100-mL round-bottom flask was added methyltriphenylphosphonium bromide (2.57 g,7.2 mmol, 3.0 equiv) and THF (36 mL). Temperature was reduced to 0 °C, then KO*t*Bu (0.81 g, 7.2 mmol, 3.0 equiv) was added and stirred for 30 minutes. Cyclopropyl(phenyl)methanone (350 mg, 2.39 mmol, 1.0 equiv) was next slowly added to the ylide solution and stirred for 1.5 hours. The reaction was quenched with DI H_2O (10 mL) and the aqueous layer was extracted with ethyl acetate (10mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and the filtrate concentrated in vacuo. Purification by flash column chromatography (1% ethyl acetate-hexanes) gave **88** as a colorless oil (130 mg, 0.98 mmol, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66–7.61 (m, 2H), 7.41–7.35 (m, 1H), 7.34–7.29 (m, 1H), 5.32 (d, *J* = 1.6 Hz, 1H), 5.01–4.94 (m, 1H), 1.73–1.65 (m, 1H), 0.92–0.84 (m, 2H), 0.67–0.60 (m, 2H).



91

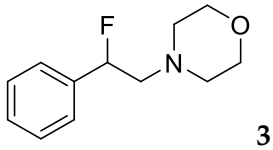
(*E*)-(2-Cyclopropylvinyl)benzene

Prepared following a previously reported method[42] with modifications. Cyclopropylacetylene (0.83 mL, 10.0 mmol, 2.0 equiv) was added to a 10-mL round-bottom flask and vacuum purged and backfilled with N_2 x3. Catecholborane (1.1 mL, 10 mmol, 2.0 equiv) was added, the reaction heated to 70 °C, stirred for 3 h, then allowed to cool to room temperature. To another 200-mL round-bottom flask was added tetrakis (triphenylphosphine)palladium (116 mg, 0.1 mmol, 0.02 equiv), DME (40 mL), and iodobenzene (0.56 mL, 5.0 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 20 minutes, at which point the crude boronate ester was added, followed by a solution of K_2CO_3 (0.69 g, 5.0 mmol, 1.0 equiv) in DI H_2O (12 mL). The reaction was refluxed for 16 hours, then cooled to room temperature and quenched with a saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted with diethyl ether (50 mL x 3) and the combined organic layers were washed with brine (60 mL), dried over Na2SO4, and the filtrate concentrated in vacuo. Purification by column chromatography (20% ethyl acetate-hexanes) gave **91** as a colorless oil (478 mg, 66%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32–7.27 (m, 4H), 7.19–7.14 (m, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 5.74 (dd, *J* = 15.8, 8.9 Hz, 1H), 1.62–1.52 (m, 2H), 0.85–0.80 (m, 2H), 0.53–0.49 (m, 2H).

4.3 Synthesis and Characterization Data for Products

*Established standard procedure for the alkene aminofluorination reaction (**GP1**):*

To a 10-mL fluorinated ethylene propylene (FEP) tube with Teflon-coated micro stir bar was added *O*-benzoylhydroxylamine (0.2 mmol, 1 equiv) and copper(II) acetate (1.82 mg, 0.01 mmol, 5 mol%), followed by addition of 1,2-dichloroethane (1.0 mL), olefin (0.4 mmol, 2 equiv) and $Et_3N \bullet 3HF$ (652 μL, 2.0 mmol, 20 equiv). The mixture was closed with an FEP screw-on cap and stirred under heat (80 °C) for 2 hours or until the consumption of *O*-benzoylhydroxylamine, verified by TLC analysis. The resulting reaction mixture was cooled to room temperature and quenched by filtration through a plug (5 mL) of activated, neutral Al_2O_3 (Brockman grade I, 58–60Å). The filtrate was concentrated under reduced pressure, providing the crude reaction mixture. The crude reaction mixture was then purified by silica column chromatography.

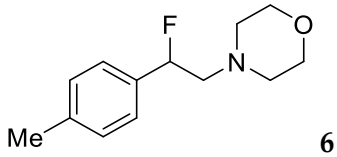


3

4-(2-Fluoro-2-phenylethyl)morpholine

Preparation via **GP1** gave **3** as a pale oil (15.9 mg, 38%). R_f = 0.12 (30% ethyl acetate-hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H), 5.66 (ddd, *J* = 48.9, 8.8, 2.4 Hz, 1H), 3.78–3.73 (m, 4H), 2.94 (ddd, *J* = 17.4, 14.2, 8.8 Hz, 1H), 2.63–2.49 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.72 (d, $J_{C\text{-}F}$ = 20.6 Hz), 128.48 (2C), 128.46 (2C), 125.59 (d, $J_{C\text{-}F}$ = 6.9 Hz), 92.62 (d, $J_{C\text{-}F}$ = 173.68 Hz), 66.93 (2C), 64.94 (d, $J_{C\text{-}F}$ = 23.1 Hz), 54.08 (2C). ^{19}F NMR

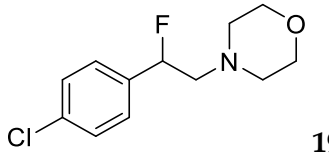
(471 MHz, $CDCl_3$) δ -176.92 (ddd, *J* = 50.1, 34.4, 17.4 Hz). FTIR (thin film): cm^{-1} 2956, 2854, 2809, 1495, 1452, 1115, 1008, 914, 727, 698. HRMS-ESI (m/z) Calculated for ($C_{12}H_{17}FNO$) ($[M+H]^+$): 210.1289; found: 210.1291.



6

4-(2-Fluoro-2-(p-tolyl)ethyl)morpholine

Preparation via **GP1** gave **6** as a pale-yellow oil (21.9 mg, 49%). R_f = 0.14 (30% ethyl acetate-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.62 (ddd, *J* = 48.9, 8.8, 2.4 Hz, 1H), 3.77–3.72 (m, 4H), 2.91 (ddd, *J* = 17.1, 14.2, 8.8 Hz, 1H), 2.68–2.53 (m, 5H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.30, 135.73 (d, J_{C-F} = 20.0 Hz), 129.13 (2C), 125.56 (2C), 92.56 (d, J_{C-F} = 173.0 Hz), 66.91 (2C), 64.88 (d, J_{C-F} = 23.4 Hz), 54.07 (2C), 21.14. ^{19}F NMR (471 MHz, $CDCl_3$) δ -174.96 (ddd, *J* = 50.1, 34.2, 17.1 Hz). FTIR (thin film): cm^{-1} 2955, 2854, 2808, 1453, 1138, 1115, 1008, 869, 816, 536. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO$) ($[M+H]^+$): 224.1445; found: 224.1451.

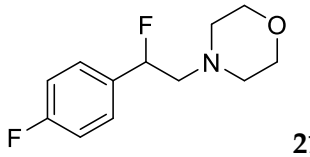


19

4-(2-(4-Chlorophenyl)-2-fluoroethyl)morpholine

Preparation via **GP1** gave **19** as a pale oil (15.6 mg, 32%). R_f = 0.12 (30% ethyl acetate-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H),

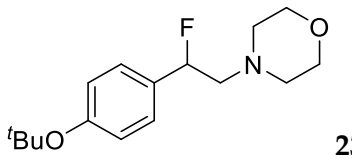
5.47 (ddd, J = 48.5, 8.5, 2.6 Hz, 1H), 3.56–3.61 (m, 4H), 2.72 (ddd, J = 17.6, 14.2, 8.5 Hz, 1H), 2.61–2.31 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.23 (d, $J_{C\text{-}F}$ = 20.4 Hz), 134.29, 128.68 (2C), 126.94 (2C), 91.97 (d, $J_{C\text{-}F}$ = 174.4 Hz), 66.89 (2C), 64.68 (d, $J_{C\text{-}F}$ = 23.3 Hz), 54.08 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -177.32 (ddd, J = 49.4, 32.8, 17.6 Hz). FTIR (thin film): cm^{-1} 2956, 2854, 2809, 1493, 1453, 1115, 1091, 1010, 880, 824, 719, 537. HRMS-ESI (m/z) Calculated for ($C_{12}H_{16}ClFNO$) ([M+H]$^+$): 244.0899; found: 244.0906.



21

4-(2-Fluoro-2-(4-fluorophenyl)ethyl)morpholine

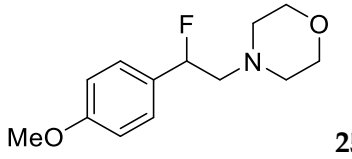
Preparation via **GP1** gave **21** as a pale oil (15.0 mg, 33%). R_f = 0.10 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.0, 5.6 Hz, 2H), 7.08–7.03 (m, 2H), 5.62 (ddd, J = 48.5, 8.6, 2.8 Hz, 1H), 3.79–3.66 (m, 4H), 2.89 (ddd, J = 17.3, 14.2, 8.6 Hz, 1H), 2.67–2.54 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.68 (dd, $J_{C\text{-}F}$ = 247.0, 2.1 Hz), 134.57 (dd, $J_{C\text{-}F}$ = 20.6, 3.2 Hz), 127.40 (dd, $J_{C\text{-}F}$ = 8.1, 6.9 Hz, 2C), 115.43 (d, $J_{C\text{-}F}$ = 21.6 Hz, 2C), 92.05 (d, $J_{C\text{-}F}$ = 173.8 Hz), 66.90 (2C), 64.75 (d, $J_{C\text{-}F}$ = 23.4 Hz), 54.08 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.29– -113.37 (m), -175.08 (ddd, J = 49.4, 33.1, 17.4 Hz). FTIR (thin film): cm^{-1} 2957, 2855, 2810, 1605, 1511, 1454, 1222, 1115, 1009, 834, 539. HRMS-ESI (m/z) Calculated for ($C_{12}H_{16}F_2NO$) ([M+H]$^+$): 228.1195; found: 228.1201.



23

4-(2-(4-(*tert*-Butoxy)phenyl)-2-fluoroethyl)morpholine

Preparation via **GP1** gave **23** as a yellow oil (16.9 mg, 30%). R_f = 0.13 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.61 (ddd, *J* = 48.8, 8.9, 2.5 Hz, 1H), 3.77–3.70 (m, 4H), 2.92 (ddd, *J* = 17.0, 14.2, 8.9 Hz, 1H), 2.70–2.53 (m, 5H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.70 (d, $J_{C\text{-}F}$ = 2.1 Hz), 133.39 (d, $J_{C\text{-}F}$ = 20.2 Hz), 126.38 (d, $J_{C\text{-}F}$ = 6.4 Hz, 2C), 124.00 (2C), 92.49 (d, $J_{C\text{-}F}$ = 172.6 Hz), 78.72, 66.95 (2C), 64.81 (d, $J_{C\text{-}F}$ = 23.5 Hz), 54.12 (2C), 28.82 (3C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -173.54 (ddd, *J* = 50.0, 34.2, 17.0 Hz). FTIR (thin film): cm^{-1} 2974, 2854, 2808, 1719, 1508, 1365, 1236, 1160, 1116, 895, 853, 549. HRMS-ESI (m/z) Calculated for ($C_{16}H_{25}FNO_2$) ($[M+H]^+$): 282.1864; found: 282.1869.

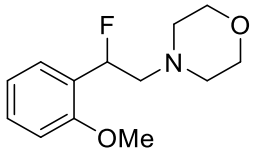


25

4-(2-Fluoro-2-(4-methoxyphenyl)ethyl)morpholine

Preparation via **GP1** gave **25** as a yellow oil (12.0 mg, 25%). R_f = 0.10 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.60 (ddd, *J* = 48.7, 8.8, 2.7 Hz, 1H), 3.81 (s, 3H), 3.72–3.76 (m, 4H), 2.92 (ddd, *J* = 16.7, 14.1, 8.8 Hz, 1H), 2.73–2.46 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.79, 130.81 (d, $J_{C\text{-}F}$ =

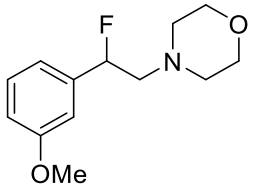
20.3 Hz), 127.14 (d, $J_{C\text{-}F}$ = 6.2 Hz 2C), 113.88 (2C), 92.41 (d, J = 172.3 Hz), 66.93 (2C), 64.74 (d, $J_{C\text{-}F}$ = 24.0 Hz), 55.27, 54.09 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -172.09 (ddd, J = 49.5, 33.5, 16.8 Hz). FTIR (thin film): cm^{-1} 2956, 2853, 2810, 1613, 1515, 1248, 1116, 1033, 832. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO_2$) ([M+H]$^+$): 240.1394; found: 240.1400.



27

4-(2-fluoro-2-(2-methoxyphenyl)ethyl)morpholine

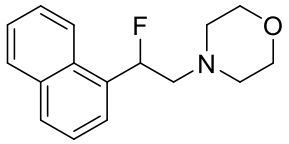
Preparation via **GP1** gave **27** as a yellow oil (18.4 mg, 38%). R_f = 0.12 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 1H), 7.34–7.27 (m, 1H), 7.02–6.97 (m, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.04 (ddd, J = 49.1, 8.8, 1.8 Hz, 1H), 3.83 (s, 3H), 3.76 (m, 4H), 2.80 (ddd, J = 19.3, 14.2, 8.8 Hz, 1H), 2.72–2.55 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30 (d, $J_{C\text{-}F}$ = 5.6 Hz), 129.18 (d, $J_{C\text{-}F}$ = 1.4 Hz), 127.32, 125.94 (d, $J_{C\text{-}F}$ = 9.6 Hz), 120.64, 110.18, 87.94 (d, $J_{C\text{-}F}$ = 171.9 Hz), 66.95 (2C), 63.81 (d, $J_{C\text{-}F}$ = 22.5 Hz), 55.28, 53.96 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -185.02 (ddd, J = 48.8, 37.3, 19.4 Hz). FTIR (thin film): cm^{-1} 2955, 2853, 1601, 1586, 1490, 1454, 1288, 1267, 1116, 1034, 869, 783, 698. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO_2$) ([M+H]$^+$): 240.1394; found: 240.1400.



29

4-(2-Fluoro-2-(3-methoxyphenyl)ethyl)morpholine

Preparation via **GP1** gave **29** as a pale oil (12.0 mg, 25%). R_f = 0.10 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 6.92–6.84 (m, 3H), 5.63 (ddd, *J* = 49.0, 8.8, 2.5 Hz, 1H), 3.82 (s, 3H), 3.77–3.73 (m, 4H), 2.90 (ddd, *J* = 17.6, 14.3, 8.8 Hz, 1H), 2.72–2.53 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.70, 140.32 (d, J_{C-F} = 20.0 Hz), 129.57, 117.72, 113.86 (d, J_{C-F} = 1.4 Hz), 111.05 (d, J_{C-F} = 7.5 Hz), 92.50 (d, J_{C-F} = 174.4 Hz), 66.93 (2C), 64.94 (d, J_{C-F} = 22.9 Hz), 55.24, 54.07 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -177.11 (ddd, *J* = 49.3, 34.5, 17.6 Hz). FTIR (thin film): cm^{-1} 2956, 2853, 2807, 1603, 1493, 1241, 1116, 1031, 754. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO_2$) ([M+H]$^+$): 240.1394; found: 240.1401.

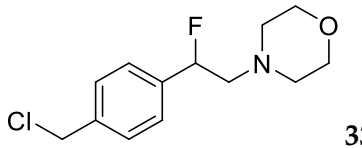


31

4-(2-Fluoro-2-(naphthalen-1-yl)ethyl)morpholine

Preparation via **GP1** gave**31** as a pale oil (10.4 mg, 20%). R_f = 0.20 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.59–7.47 (m, 3H), 6.42 (ddd, *J* = 48.4, 8.7, 2.1 Hz, 1H), 3.82–3.78 (m, 4H), 3.02 (ddd, *J* = 19.0, 14.6, 8.7 Hz, 1H), 2.86 (ddd, *J* = 36.0, 14.6, 2.1 Hz, 1H), 2.78–2.58 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.41 (d, J_{C-F} = 18.7 Hz), 133.60, 129.58 (d, J_{C-F} = 4.1 Hz), 129.02, 128.85 (d, J_{C-F} = 1.3 Hz), 126.46, 125.77, 125.30, 123.19 (d, J_{C-F} = 11.2 Hz), 122.62, 91.00 (d, J_{C-F} = 174.2 Hz), 66.97 (2C), 64.57 (d, *J* = 22.7 Hz), 54.11 (2C). ^{19}F NMR (471 MHz, $CDCl_3$) δ -180.15 (ddd, *J* = 48.2, 35.9, 19.0 Hz).

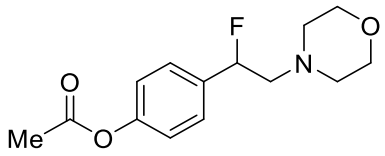
FTIR (thin film): cm^{-1} 3050, 2955, 2853, 2809, 1675, 1452, 1137, 1009, 798, 775. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO_2$) ([M+H]$^+$): 260.1445; found: 260.1449.



33

4-(2-(4-(Chloromethyl)phenyl)-2-fluoroethyl)morpholine

Preparation via **GP1** gave **33** as a yellow oil (14.9 mg, 29%). R_f = 0.16 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.67 (ddd, *J* = 48.7, 8.7, 2.6 Hz, 0H), 4.58 (s, 2H), 3.76–3.74 (m, 4H), 2.89 (ddd, *J* = 17.4, 14.2, 8.7 Hz, 1H), 2.76–2.54 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.92 (d, $J_{C\text{-}F}$ = 20.1 Hz), 137.73, 128.72 (2C), 125.87 (d, $J_{C\text{-}F}$ = 7.0 Hz 2C), 92.22 (d, $J_{C\text{-}F}$ = 174.3 Hz), 66.85 (2C), 64.78 (d, $J_{C\text{-}F}$ = 23.0 Hz), 54.04 (2C), 45.72. ^{19}F NMR (471 MHz, $CDCl_3$) δ -177.62 (ddd, *J* = 50.4, 33.9, 17.6 Hz). FTIR (thin film): cm^{-1} 2984, 2843, 2801, 1493, 1350, 1123, 1056, 968, 867, 813, 727. HRMS-ESI (m/z) Calculated for ($C_{13}H_{18}ClFNO$) ([M+H]+): 258.1056; found: 258.1061.

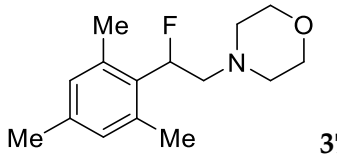


35

4-(1-Fluoro-2-morpholinoethyl)phenyl acetate

Preparation via **GP1** gave **35** as a pale oil (7.0 mg, 13%). R_f = 0.11 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H),

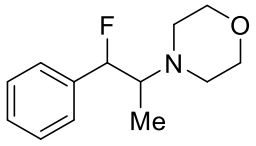
5.65 (ddd, J = 48.6, 8.7, 2.3 Hz, 1H), 3.76–3.74 (m, 4H), 2.89 (ddd, J = 17.4, 14.2, 8.7 Hz, 1H), 2.72–2.53 (m, 5H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.35, 150.65, 136.29 (d, $J_{C\text{-}F}$ = 20.4 Hz), 126.72 (2C), 121.68 (2C), 92.15 (d, $J_{C\text{-}F}$ = 174.2 Hz), 66.91 (2C), 64.83 (d, $J_{C\text{-}F}$ = 23.1 Hz), 54.08 (2C), 21.10. ^{19}F NMR (471 MHz, $CDCl_3$) δ -176.31 (ddd, J = 50.3, 33.9, 17.4 Hz). FTIR (thin film): cm^{-1} 2929, 2854, 1755, 1509, 1369, 1191, 1116, 1009, 911, 882, 869. HRMS-ESI (m/z) Calculated for ($C_{14}H_{19}FNO_3$) ([M+H]$^+$): 268.1344; found: 268.1350.



37

4-(2-Fluoro-2-mesitylethyl)morpholine

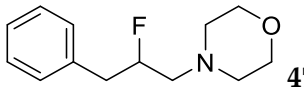
Preparation via **GP1** gave **37** as a pale oil (7.5 mg, 15%). R_f = 0.14 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 6.03 (ddd, J = 48.4, 9.3, 2.7 Hz, 1H), 3.78–3.74 (m, 4H), 3.15 (td, J = 14.4, 9.3 Hz, 1H), 2.67–2.57 (m, 4H), 2.50 (ddd, J = 33.1, 14.4, 2.7 Hz, 1H), 2.38–2.34 (m, 6H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.70, 135.67 (d, $J_{C\text{-}F}$ = 3.6 Hz 2C), 131.44 (d, $J_{C\text{-}F}$ = 17.8 Hz), 129.97 (2C), 90.70 (d, $J_{C\text{-}F}$ = 172.9 Hz), 66.95 (2C), 62.16 (d, $J_{C\text{-}F}$ = 22.7 Hz), 54.07 (2C), 20.78, 20.40, 20.37. ^{19}F NMR (471 MHz, $CDCl_3$) δ -181.67 (ddd, J = 48.1, 33.1, 14.7 Hz). FTIR (thin film): cm^{-1} 2959, 2854, 2809, 1678, 1612, 1452, 1142, 1116, 1050, 1007, 871, 852, 731, 572. HRMS-ESI (m/z) Calculated for ($C_{15}H_{23}FNO$) ([M+H]$^+$): 252.1758; found: 252.1765.



39

4-(1-Fluoro-1-phenylpropan-2-yl)morpholine

Preparation via **GP1** gave **39** as a 1:1 mixture of diastereomers, pale oil (15.6 mg, 35%). R_f= 0.15 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 10H), 5.72 (dd, *J* = 48.1, 3.0 Hz, 1H), 5.35 (dd, *J* = 47.5, 7.4 Hz, 1H), 3.77–3.64 (m, 8H), 3.03 (dt, *J* = 14.0, 7.4 Hz, 1H), 2.83 (dqd, *J* = 26.4, 7.4, 3.0 Hz, 1H), 2.77–2.60 (m, 8H), 1.04 (dd, *J* = 6.9, 1.6 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.42 (d, J_{C-F} = 20.6 Hz), 138.49 (d, J_{C-F} = 19.9 Hz), 128.46 (d, J_{C-F} = 2.1 Hz), 128.29 (2C), 128.15 (2C), 127.66 (d, J_{C-F} = 1.3 Hz), 126.62 (d, J_{C-F} = 6.4 Hz, 2C), 125.05 (d, J_{C-F} = 8.7 Hz, 2C), 95.71 (d, J_{C-F} = 176.5 Hz), 94.66 (d, J_{C-F} = 178.8 Hz), 67.54 (2C), 67.42 (2C), 64.88 (d, J_{C-F} = 21.8 Hz), 63.42 (d, J_{C-F} = 21.6 Hz), 49.88 (2C), 49.58 (2C), 11.19 (d, J_{C-F} = 6.1 Hz), 7.59 (d, J_{C-F} = 6.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.20 (dd, *J* = 47.5, 13.6 Hz). FTIR (thin film): cm^{-1} 2956, 2852, 1451, 1377, 1146, 1115, 1029, 984, 751, 699, 525. HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO$) ($[M+H]^+$): 224.1445; found: 224.1451.

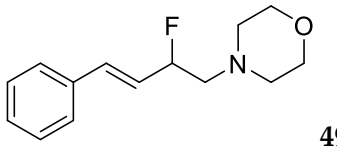


47

4-(2-Fluoro-3-phenylpropyl)morpholine

Preparation via **GP1** gave **47** as the sole fluorinated product in low yield (<5%) as an inseparable mixture with undesired side products. R_f= 0.05 (50% ethyl acetate-hexanes).

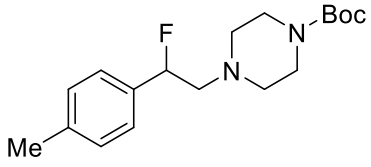
^{19}F NMR (471 MHz, $CDCl_3$) δ -178.42 (ddddd, *J* = 48.6, 28.4, 22.7, 21.1, 19.8 Hz). HRMS-ESI (m/z) Calculated for ($C_{13}H_{19}FNO$) ([M+H]$^+$): 224.1445; found: 224.1451.



49

(*E*)-4-(2-fluoro-4-phenylbut-3-en-1-yl)morpholine

Preparation via **GP1** gave **49** as a yellow oil (4.3 mg, 9%). R_f = 0.24 (15% MeOH, 30% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.38 (m, 2H), 7.36–7.32 (m, 2H), 7.30–7.27 (m, 1H), 6.71 (dd, *J* = 16.0, 3.5 Hz, 1H), 6.24 (ddd, *J* = 16.0, 13.4, 6.5 Hz, 1H), 5.38–5.22 (m, 1H), 3.81–3.72 (m, 4H), 2.81 (ddd, *J* = 18.1, 14.0, 8.0 Hz, 1H), 2.72–2.66 (m, 1H), 2.67–2.58 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.89, 133.21 (d, $J_{C\text{-}F}$ = 11.61), 129.88 (2C), 128.65 (2C), 128.42 (d, $J_{C\text{-}F}$ = 34.7 Hz), 126.89 (d, $J_{C\text{-}F}$ = 46.8 Hz), 91.60 (d, $J_{C\text{-}F}$ = 170.0 Hz), 66.84 (2C), 63.02 (d, $J_{C\text{-}F}$ = 22.4 Hz), 54.08 (2C). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -174.38 (ddddd, *J* = 48.7, 31.1, 18.1, 13.4, 3.5 Hz). FTIR (thin film): cm^{-1} 1635, 1451, 1279, 1117,1010, 745, 695. HRMS-ESI (m/z): Calculated for ($C_{14}H_{19}FNO$) ([M+H]$^+$): 236.1445; found: 236.1448.

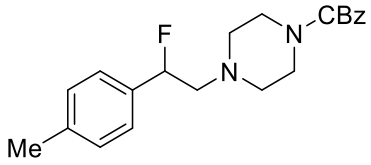


57

***tert*-Butyl 4-(2-fluoro-2-(p-tolyl)ethyl)piperazine-1-carboxylate**

Preparation via **GP1** gave **57** as a pale oil

R_f = 0.25 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.59 (ddd, *J* = 48.8, 8.8, 2.3 Hz, 1H), 3.47–3.44 (m, 4H), 2.87 (ddd, *J* = 17.1, 14.3, 8.8 Hz, 1H), 2.62–2.43 (m, 5H), 2.27 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.68, 138.30, 135.72 (d, J_{C-F} = 20.0 Hz), 129.13 (2C), 125.52 (d, J_{C-F} = 6.59, 2C), 92.63 (d, J_{C-F} = 173.0 Hz), 79.58 (2C), 64.49 (d, J_{C-F} = 23.5 Hz), 53.38 (2C), 28.61 (3C), 21.37. ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.13 (ddd, *J* = 50.0, 34.0, 17.1 Hz). FTIR (thin film): cm^{-1} 2975, 2928, 2860, 2811, 1693, 1455, 1419, 1365, 1243, 1170, 1125, 1004, 816. HRMS-ESI (m/z) Calculated for ($C_{17}H_{25}FNO_2$) ([M+H]$^+$): 294.1864; found: 294.1869.

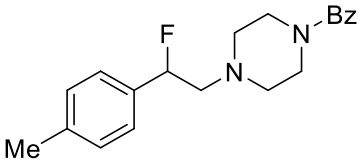


59

2-(4-(2-Fluoro-2-(p-tolyl)ethyl)piperazin-1-yl)-1-phenyl-2-ethan-1-one

Preparation via **GP1** gave **59** as a yellow oil (26.2 mg, 37%). R_f = 0.38 (50% ethyl aceteate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.30 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.61 (ddd, *J* = 48.8, 8.8, 2.3 Hz, 1H), 5.14 (s, 2H), 3.75–3.45 (m, 4H), 2.93 (ddd, *J* = 17.0, 14.3, 8.8 Hz, 1H), 2.71–2.62 (m, 1H), 2.61–2.57 (m, 4H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.16, 138.37, 136.66, 135.60 (d, J_{C-F} = 20.1 Hz), 129.15 (2C), 128.46 (2C), 127.98, 127.86 (2C), 125.52 (d, J_{C-F} = 6.7 Hz, 2C), 92.61 (d, J_{C-F} = 173.3 Hz), 67.10, 64.38 (d, J_{C-F} = 23.6 Hz), 53.26 (2C), 43.75, 21.14. ^{19}F NMR ($CDCl_3$, 471 MHz): δ -175.14 (ddd, J = 49.9, 33.8, 17.1 Hz). FTIR (thin film): cm^{-1} 1696, 1455, 1428, 1235, 1123, 1003, 762, 697. HRMS-ESI (m/z): Calculated for ($C_{21}H_{26}FN_2O_2$) ([M+H]$^+$): 357.1973; found:

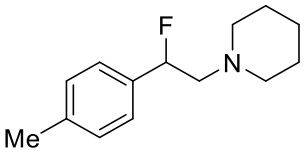
357.1977.



61

(4-(2-Fluoro-2-(p-tolyl)ethyl)piperazin-1-yl)(phenyl)methanone

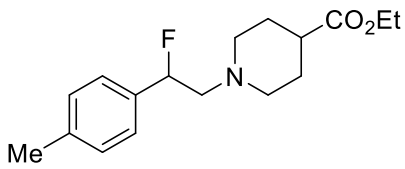
Preparation via **GP1** gave **61** as a yellow oil (28.6 mg, 44%). R_f = 0.40 (50% ethyl aceteate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.62 (ddd, *J* = 48.8, 8.7, 2.3 Hz, 1H), 3.82 (br, 2H), 3.46 (br, 2H), 2.94 (ddd, *J* = 17.0, 14.3, 8.7 Hz, 1H), 2.79–2.46 (m, 5H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.25, 138.40 (d, J_{C-F} = 1.8 Hz), 135.71, 135.50 (d, J_{C-F} = 20.0 Hz), 129.64, 129.16 (2C), 128.43 (2C), 127.00 (2C), 125.50 (d, J_{C-F} = 6.6 Hz, 2C), 92.62 (d, J_{C-F} = 173.2 Hz), 64.21 (d, J_{C-F} = 23.6 Hz), 53.82, 53.29, 47.62, 42.11, 21.14. ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.16 (ddd, *J* = 49.8, 33.7, 17.1 Hz). FTIR (thin film): cm^{-1} 1648, 1414, 1406, 1215, 1114, 754, 598. HRMS-ESI (m/z): Calculated for ($C_{20}H_{24}FN_2O$) ($[M+H]^+$): 327.1867; found: 327.1872.



65

1-(2-Fluoro-2-(p-tolyl)ethyl)piperidine

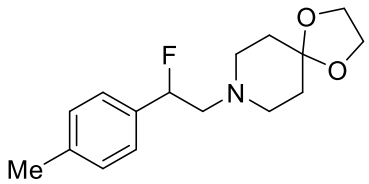
Preparation via **GP1** gave **65** in low yield (5%) as an inseparable mixture with undesired side products. ^{19}F NMR (471 MHz, $CDCl_3$) δ -174.76 (ddd, *J* = 50.9, 35.3, 17.3 Hz). HRMS-ESI (m/z): Calculated for ($C_{14}H_{21}FN$) ($[M+H]^+$): 222.1653; found: 222.1657.



67

Ethyl 1-(2-fluoro-2-(p-tolyl)ethyl)piperidine-4-carboxylate

Preparation via **GP1** gave **67** as a pale-yellow oil (10.3 mg, 18%). R_f = 0.27 (50% ethyl aceteate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.61 (ddd, *J* = 48.8, 8.7, 2.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 11.4 Hz, 1H), 2.95 (d, *J* = 11.4 Hz, 1H), 2.90 (ddd, *J* = 17.2, 14.3, 8.7 Hz, 1H), 2.61 (ddd, *J* = 34.0, 14.3, 2.5 Hz, 1H), 2.35 (s, 3H), 2.29–2.17 (m, 3H), 1.95–1.88 (m, 2H), 1.87–1.75 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl) δ 175.05, 138.19 (d, J_{C-F} = 1.9 Hz), 136.03 (d, J_{C-F} = 20.1 Hz), 129.10 (2C), 125.53 (d, J_{C-F} = 6.7 Hz, 2C), 92.68 (d, J_{C-F} = 172.9 Hz), 64.74 (d, J_{C-F} = 23.6 Hz), 60.28 (2C), 53.44, 53.36, 40.92, 28.25, 21.16, 14.20. ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.00 (ddd, *J* = 49.9, 33.9, 17.0 Hz). FTIR (thin film): cm^{-1} 2944, 2803, 1729, 1515, 1448, 1284, 1181, 1047, 816, 527. HRMS-ESI (m/z): Calculated for ($C_{17}H_{25}FNO_2$) ([M+H]$^+$): 294.1864; found: 294.1869.

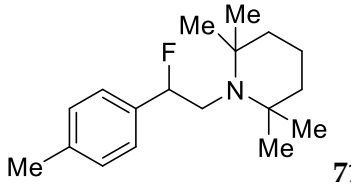


69

8-(2-Fluoro-2-(p-tolyl)ethyl)-1,4-dioxa-8-azaspiro[4.5]decane

Preparation via **GP1** gave **69** as a colorless oil (11.7 mg, 21%). R_f = 0.62 (15% MeOH, 30% ethyl acetate-hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* =

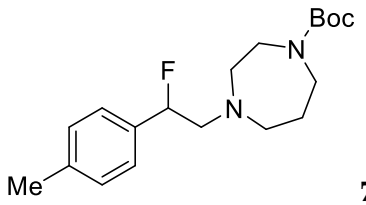
8.0 Hz, 2H), 5.61 (ddd, J = 49.6, 8.9, 2.3 Hz, 1H), 3.96 (s, 4H), 2.95 (ddd, J = 17.2, 14.3, 8.9 Hz, 1H), 2.70 (br. s, 4H), 2.66–2.57 (m, 1H), 2.35 (s, 3H), 1.84–1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.20 (d, J_{C-F} = 1.6 Hz), 136.00 (d, J_{C-F} = 19.9 Hz), 129.11 (2C), 125.53 (d, J_{C-F} = 6.5 Hz, 2C), 106.97, 92.74 (d, J_{C-F} = 172.9 Hz), 64.20 (2C), 64.17 (d, J_{C-F} = 23.6 Hz), 51.82 (2C), 34.79 (2C), 21.16. ^{19}F NMR ($CDCl_3$, 471 MHz): δ -175.34 (ddd, J = 49.6, 34.4, 17.2 Hz). FTIR (thin film): cm^{-1} 1143, 1094, 1039, 964, 946, 915, 818. HRMS-ESI (m/z): Calculated for ($C_{16}H_{23}FNO_2$) ([M+H]$^+$): 280.1707; found: 280.1714.



71

1-(2-Fluoro-2-(p-tolyl)ethyl)-2,2,6,6-tetramethylpiperidine

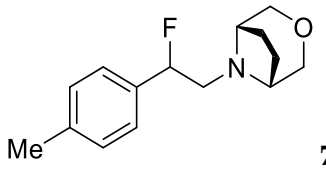
Preparation via **GP1** gave **71** as a colorless oil (7.5 mg, 14%). R_f = 0.20 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.36 (ddd, J = 48.8, 8.9, 2.5 Hz, 1H), 2.99 (td, J = 16.6, 8.9 Hz, 1H), 2.67 (ddd, J = 33.9, 16.6, 2.5 Hz, 1H), 2.36 (s, 3H), 1.63–1.41 (m, 6H), 1.09 (s, 6H), 1.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.90, 137.09 (d, J_{C-F} = 20.7 Hz), 129.04 (2C), 125.52 (d, J_{C-F} = 6.7 Hz, 2C), 97.08 (d, J_{C-F} = 173.8 Hz), 54.84 (2C), 52.08 (d, J_{C-F} = 24.7 Hz), 41.07 (4C), 29.70 (2C), 21.18, 17.82. ^{19}F NMR (471 MHz, $CDCl_3$) δ -178.16 (ddd, J = 49.8, 33.8, 17.2 Hz). FTIR (thin film): cm^{-1} 2954, 2926, 2851, 2804, 1493, 1274, 1114, 1005, 862, 740, 699. HRMS-ESI (m/z): Calculated for ($C_{18}H_{29}FN$) ([M+H]$^+$): 278.2279; found: 278.2283.



73

***tert*-B utyl 4-(2-fluoro-2-(p-tolyl)ethyl)-1,4-diazepane-1-carboxylatez**

Preparation via **GP1** gave **73** as a colorless oil (14.6 mg, 22%). R_f = 0.27 (30% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.54 (ddd, *J* = 48.6, 8.3, 2.2 Hz, 1H), 3.52–3.39 (m, 4H), 3.04 (ddd, *J* = 16.6, 14.5, 8.3 Hz, 1H), 2.86–2.72 (m, 5H), 2.35 (s, 3H), 1.86–1.76 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.56, 155.43, 138.15 (d, $J_{C\text{-}F}$ = 7.0 Hz), 135.94 (d, $J_{C\text{-}F}$ = 19.9 Hz), 129.07 (2C), 125.52 (d, $J_{C\text{-}F}$ = 6.6 Hz, 2C), 93.23 (d, $J_{C\text{-}F}$ = 173.0 Hz), 93.18 (d, $J_{C\text{-}F}$ = 173.4 Hz), 79.26, 76.75, 63.21, 63.02, 56.26, 56.06, 55.21, 55.04, 46.91, 46.35, 45.98, 45.07, 28.46 (9C), 27.89, 27.72, 21.14. (Mixture of cis–trans amide rotamers). ^{19}F NMR (471 MHz, $CDCl_3$) δ -176.80 (ddd, *J* = 49.2, 32.4, 16.9 Hz), -177.01 (ddd, *J* = 48.5, 32.4, 17.0 Hz). (Mixture of cis–trans amide rotamers). FTIR (thin film): cm^{-1} 2930, 1688, 1460, 1411, 1157, 903, 726. HRMS-ESI (m/z): Calculated for ($C_{19}H_{30}FN_2O_2$) ([M+H]$^+$): 337.2286; found: 337.2289.

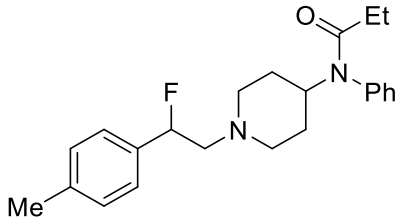


75

8-(2-Fluoro-2-phenylethyl)-3-oxa-8-azabicyclo[3.2.1]octane

Preparation via **GP1** gave **75** as a pale-yellow oil (20.5 mg, 41%). R_f = 0.10 (30% ethyl

acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.57 (ddd, *J* = 48.4, 8.1, 3.1 Hz, 1H), 3.76 (dd, *J* = 14.4, 10.4 Hz, 2H), 3.49 (ddd, *J* = 12.6, 10.4, 1.9 Hz, 2H), 3.28–3.24 (m, 1H), 3.00–2.93 (m, 1H), 2.81 (ddd, *J* = 17.9, 14.1, 8.1 Hz, 1H), 2.51 (ddd, *J* = 31.7, 14.1, 3.1 Hz, 1H), 2.36 (s, 3H), 1.98–1.78 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.21 (d, $J_{C\text{-}F}$ = 1.9 Hz), 136.00 (d, $J_{C\text{-}F}$ = 20.1 Hz), 129.04 (2C), 125.66 (d, $J_{C\text{-}F}$ = 6.7 Hz, 2C), 94.80 (d, $J_{C\text{-}F}$ = 172.0 Hz), 73.11, 73.06, 62.06, 61.77 (d, $J_{C\text{-}F}$ = 2.2 Hz), 60.34 (d, $J_{C\text{-}F}$ = 23.7 Hz), 25.09, 24.75, 21.16. ^{19}F NMR (471 MHz, $CDCl_3$) δ -176.72 (ddd, *J* = 49.0, 31.7, 17.8 Hz). FTIR (thin film): cm^{-1} 2946, 2855, 1516, 1182, 1132, 1008, 981, 883, 816, 641, 543. HRMS-ESI (m/z): Calculated for ($C_{15}H_{21}FNO$) ($[M+H]^+$): 250.1602; found: 250.1608.

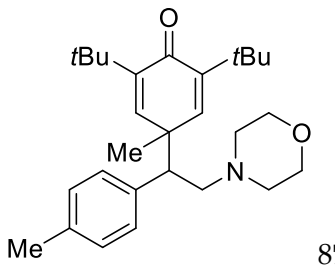


8**6**

***N*-(1-(2-Fluoro-2-(p-tolyl)ethyl)piperidin-4-yl)-N-phenylpropionamide**

Preparation via **GP1** gave 8**6** as a pale oil (20.2 mg, 27%). R_f = 0.42 (50% ethyl acetate-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.32 (m, 3H), 7.20–7.12 (m, 4H), 7.08 (d, *J* = 6.9 Hz, 2H), 5.52 (ddd, *J* = 49.1, 9.2, 2.1 Hz, 1H), 4.68 (tt, *J* = 12.3, 3.9 Hz, 1H), 3.10–2.98 (m, 2H), 2.86 (ddd, *J* = 16.9, 14.4, 9.2 Hz, 1H), 2.52 (ddd, *J* = 35.8, 14.3, 2.1 Hz, 1H), 2.37–2.21 (m, 5H), 1.92 (q, *J* = 7.4 Hz, 2H), 1.84–1.73 (m, 2H), 1.54–1.39 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.54, 138.83, 138.25, 135.83 (d, $J_{C\text{-}F}$ = 20.0 Hz),

130.43 (2C), 129.28 (2C), 129.12 (2C), 128.26, 125.48 (d, $J_{C\text{-}F}$ = 6.5 Hz, 2C), 92.49 (d, J = 173.1 Hz), 64.58 (d, J = 23.2 Hz), 53.92, 53.29, 51.96, 30.52 (2C), 28.49, 21.14, 9.59. ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.23 (ddd, J = 50.6, 35.7, 16.9 Hz). FTIR (thin film): cm^{-1} 2937, 2808, 1652, 1595, 1494, 1376, 1261, 1055, 816, 705, 530. HRMS-ESI (m/z): Calculated for ($C_{23}H_{30}FN_2O$) ([M+H]$^+$): 369.2337; found: 369.2341.

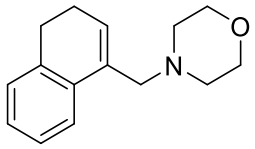


87

2,6-Di-*tert*-butyl-4-methyl-4-(2-morpholino-1-(p-tolyl)ethyl)cyclohexa-2,5-dien-1-one

To a standard reaction was added butylated hydroxytoluene (44.1 mg, 0.2 mmol, 1.0 equiv). Following the standard protocol, purification by flash column chromatography (20% ethyl acetate-hexanes) gave **87** as a yellow oil (28.7 mg, 34%). R_f = 0.31 (10% MeOH, 27% ethyl acetate, 63% hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 7.9 Hz, 2H), 6.56 (d, J = 2.8 Hz, 1H), 6.43 (d, J = 2.8 Hz, 1H), 3.61–3.50 (m, 4H), 2.92 (dd, J = 8.1, 4.5 Hz, 1H), 2.53 (dd, J = 12.9, 8.1 Hz, 1H), 2.48 (dd, J = 12.9, 4.5 Hz, 1H), 2.32 (s, 3H), 2.28–2.24 (m, 4H), 1.26 (s, 9H), 1.15 (s, 9H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 186.30, 146.46, 146.36, 144.30 (2C), 137.27, 136.39, 129.15 (2C), 128.54 (2C), 66.85, 60.13 (2C), 53.94, 52.45 (2C), 42.44, 34.81, 34.76, 29.45 (3C), 29.37 (3C), 25.23, 21.00. FTIR

(thin film): cm^{-1} 1656, 1637, 1456, 1362, 1249,1118, 910, 868, 734. HRMS-ESI (m/z): Calculated for ($C_{28}H_{42}NO_2$) ([M+H]$^+$): 424.3210; found: 424.3215.



90

4-((3,4-Dihydronaphthalen-1-yl)methyl)morpholine

Following the standard procedure with **88** and purification by flash column chromatography (10% ethyl acetate-hexanes) gave **90** as a clear oil (25.0 mg, 0.11 mmol, 64%). Spectroscopic data match a previous report.[42] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.22–7.11 (m, 3H), 6.02 (t, *J* = 4.2 Hz, 1H), 3.75–3.66 (m, 4H), 3.30 (s, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 2.48 (br. s, 4H), 2.35–2.26 (m, 2H).

References

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