Published in final edited form as:

J Am Chem Soc. 2022 November 09; 144(44): 20463–20471. doi:10.1021/jacs.2c09118.

Copper-Catalyzed Three-Component Aminofluorination of Alkenes and 1,3-Dienes: Direct Entry to Diverse β-Fluoroalkylamines

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Abstract

Rapid and efficient access to structurally diverse β-fluoroalkylamines is in high demand, with their wide presence and great importance in medicinal chemistry and drug development. Direct 1,2-aminofluorination of alkenes offers an ideal strategy for one-step entry to β-fluorinated amines from readily available starting materials. Yet the synthesis of valuable β-fluorinated alkylamines remains an unsolved challenge, due to the inherent incompatibility between electrophilic fluoride sources and the electron-rich alkylamines. We report an unprecedented, catalytic, three-component aminofluorination of diverse alkenes and 1,3-dienes, which has been achieved by an innovative copper-catalyzed electrophilic amination strategy using *O*-benzoylhydroxylamines as alkylamine precursors. The use of $Et_3N{\bullet}3HF$ is also critical, not only as a commercially available and inexpensive fluoride source to enable effective fluorination but also as an acid source for the formation of aminyl radical cation for electrophilic amination. Mechanistic experiments suggest the involvement of aminyl radical species and carbon-radical intermediates under reaction conditions. This method features high regioselectivity, good tolerance of diverse functional groups, and provides a practical and direct entry to a broad range of β-fluorinated electron-rich alkylamines. Synthetic applications of this method have also been highlighted by its use for the rapid entry to β-fluoridated amine-containing pharmaceuticals, natural products, and bioactive compounds.

Graphical Abstract

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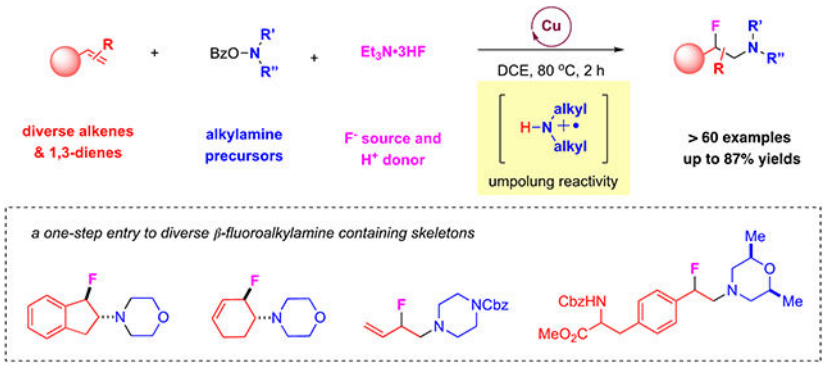
The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Condition optimizations, experimental procedures, compound characterization, and NMR spectra.



INTRODUCTION

The importance of nitrogen-containing molecules is evident by their ubiquitous presence in bioactive natural products, small-molecule probes, and pharmaceuticals. Among FDA-approved small-molecule drugs, over 80% entail at least one nitrogen atom. Therefore, rapid, efficient synthesis of novel bioactive nitrogen-containing compounds is of the utmost importance in biomedical research and drug discovery. The introduction of a fluorine to amine-containing compounds is a powerful strategy in medicinal chemistry and drug discovery that can productively influence their conformation, pK_a, physical, chemical, biological, and pharmacokinetic properties.[1-6] Particularly, β-fluorination of an amino functionality can greatly modulate the basicity of the vicinal amino group, offering dramatic enhancements in bioavailability, lipophilicity, and biological activity (Figure 1, A).[7, 8] Accordingly, β-fluoroamine motifs are highly valued in drug development and the preparation of β-fluorinated amines is in great demand.

Traditionally, the synthesis of β-fluorinated amines has typically proceeded with a multiple step sequence, e.g., through substitution reactions on aziridines, β-amino alcohols, or β-fluoroalcohols with a fluoride or amine nucleophile.[9] Alternatively, direct 1,2-aminofluorination of alkenes offers an ideal strategy allowing rapid access to β-fluorinated amines from readily available starting materials (Figure 1, B).[10-12] Extensive efforts have been devoted to alkene aminofluorination in recent years, which elegantly expedite the synthesis of vicinal aminofluorine scaffolds.[13, 14] However, the known transformations have been limited to the use of a few specially substituted electro-deficient amines for the preparation of β-fluorosulfonamides,[15-21] β-fluorocarbamates,[22-24] β-fluorosulfoximines,[25] and the use of azides to realize β-fluoroazides.[26] Despite the attractiveness of these studies, the amine functionalities introduced in these methods need to be further derivatized to access medicinally valuable entities. In sharp contrast, a one-step entry to β-fluoroalkylamines remains an unsolved synthetic challenge.[27] It is fundamentally problematic to develop such a transformation using conventionally nucleophilic alkylamines, given the inherent incompatibility of electron-rich alkylamines with electrophilic fluorination reagents or strong oxidizing conditions.[28] To overcome these obstacles, an innovative synthetic strategy is needed to realize such a desired yet challenging transformation that allows for direct access to valuable β-fluoroalkylamines.

We envision that an umpolung electrophilic amination strategy would offer an effective solution for the direct installation of electron-rich alkylamines (Figure 1, C). Such an unconventional strategy engages a different alkene activation pathway through electrophilic amination using heteroatom-substituted alkylamine precursors ($LG–NR_2$), allowing for a subsequent coupling with nucleophilic partners. Our group has recently discovered a novel alkene activation mode initiated by copper-catalyzed N—O bond cleavage of *O*-acyl *N*, *N*-dialkylhydroxylamines and electrophilic amination addition to the alkenes, and achieved a series of copper-catalyzed alkene amino oxygenation reactions.[29-31] The Morandi group has also reported elegant examples of iron-catalyzed aminochlorination using *O*-pivaloyl hydroxylamine triflic acid derivatives, conceivably through the formation of electrophilic protonated aminyl radical species.[32, 33] Although this umpolung strategy represents a highly promising new platform for alkene amino functionalization, the incorporation of different nucleophilic partners is not trivial, owing to high reactivities of the transient nitrogen or carbon radicals that can readily undergo undesired degradation and side reactions. Furthermore, the development of the aminofluorination is particularly difficult for this umpolung approach via a protonated aminyl radical species, due to the low nucleophilicity of fluoride ions in protic solvents.

Here we disclose the development of an unprecedented copper-catalyzed protocol for aminofluorination of diversely substituted alkenes and 1,3-dienes for the selective formation of a wide range of β-fluoroalkylamines using readily available *N*, *N*-dialkylhydroxylamines[34, 35] as a precursor of electron-rich alkylamines (Figure 1, D). In this study, we identified $Et_3N•3HF$ as the critical nucleophilic partner, which not only enables effective fluorination step as a convenient fluorinating agent but also contributes as an acid source for the formation of aminyl radical species that participates in the electrophilic alkene amination step. This work provides, for the first time, a catalytic aminofluorination transformation that allows for one-step installation of β-fluoro electron-rich tertiary amines onto alkenes and 1,3-dienes in a three-component manner.[36] Synthetic values of this method have been highlighted by its application to the rapid synthesis of β-fluoroamine-containing pharmaceuticals, natural products, and bioactive compounds.

RESULTS AND DISCUSSION

ALKENE AMINOFLUORINATION – CONDITION DEVELOPMENT

Our studies began with the aminofluorination of 4-methylstyrene **1a** using *O*-benzoyl-*N*-hydroxylmorpholine **2a** as the alkylamine precursor (Figure 2). First, various fluoride sources were tested including Olah's reagent, silver fluoride, cesium fluoride, and tetrabutylammonium fluoride and triethylamine trihydrofluoride ($Et_3N•c–5$). $Et_3N•3HF$, a commercially available and inexpensive fluoride source, was found to be effective in promoting the aminofluorination reaction and provide desired product **3a** in 40% yield. Observed under this condition was common byproduct **3a'** which resulted from the nucleophilic addition of benzoate leaving group. We also confirmed that **3a'** was not a competent intermediate for the formation of **3a** under reaction conditions. Encouragingly, the formation of **3a'** was suppressed by using excess $Et_3N•3HF$ (10 equiv) (entry 6). Next, we examined the effect of the leaving groups of the amine precursors in this reaction (Figure

2, B). Selected examples of the leaving group include different benzoates (**A**–**D**), acetoxy group (**E**), trichloroacetoxy (**F**), a carbonate group (**G**), a phosphinate group (**H**), and *O*-aryl hydroxylamine **(I)**. Although many of them provided desired product **3a**, none was more effective in the aminofluorination reaction than **2a** bearing a simple benzoate group (**A**). Thus, we decided to focus on the aminofluorination of **1a** using **2a** and Et_3N•3HF for further optimization (details in SI). Among varied reaction parameters, the choice of copper catalyst showed a significant effect on the reaction (Figure 2, C). Copper(II) hexafluoroacetylacetonate was found to be the most effective among various copper (I) or (II) catalysts. Even with a reduced 2.5 mol % loading, the reaction afforded **3a** in 82% yield, which was chosen as the standard conditions.

ALKENE AMINOFLUORINATION – SCOPE OF ALKENES AND AMINES

With the standard conditions established, we investigated the generality of this aminofluorination reaction on different types of alkenes and amines (Table 1). We first examined the variation of the alkene component toward the formation of β-fluoroamines **3** using **2a**. Different styrene derivatives all participated successfully in the reactions, delivering β-fluoroamines **3a–3o** in good to high yields (45–83%). Note that various substituents were well tolerated, ranging from electron-withdrawing groups (**3d–3e**), electron-donating groups (**3f–3k**), sterically encumbered 2,4,6-trimethyl groups (**3l**), to sensitive functionalities such as benzylic chloride (**3m**), acetate (**3n**) and boronic acid pinacol ester (**3o**). Aminofluorination of other vinyl arenes and heteroarenes, including naphthalene systems (**3p**–**3q**), benzothiophene (**3r**), indole (**3s**) and pyridine (**3t**), also produced the corresponding β-fluoroamine products smoothly in 33–66% yields. The reaction of simple alkyl substituted alkenes were also attempted. The desired β-fluoroamine **3u** was formed, albeit in only 12% yield, promoting us to seek for alternative route to access such alkyl-substituted β-fluoroamines (see Figure 3A in the following section). In addition to terminal alkenes, internal alkenes were also effective to produce desired products (**3v–3z**). These reactions occurred regioselectively, with the addition of the fluoride exclusively at the benzylic position. Only modest levels of diastereoselectivity were observed in the reactions of acyclic internal alkenes (**3v–3w**) while high diastereomeric ratios (up to 20:1) were obtained for cyclic alkenes (**3x–3z**). Note that the reactions of (*E*)- and (*Z*)-**1v** both led to the formation of **3v** in comparable yields with similar diastereomeric ratios. The *anti*-selectivity observed for cyclic alkenes (**3x–3z**) probably resulted from the steric influence in the fluorination step where the fluoride was installed from the opposite side of the amino group.

The scope of alkylamines in this aminofluorination reaction was found to be extensive, enabling a one-step access to diversely functionalized β-fluoroalkylamines. The reactions of different piperidine-containing aminating reagents provided the desired products **4a**–**4d**. Note that the varied efficiency between **4b** (32% yield) and **4c**–**4d** (50–60% yields) revealed a beneficial role of electron-withdrawing substituents of piperidine precursors. Other six-membered cyclic amine precursors readily participated in this reaction, such as thiomorpholine **4e** (69% yield), bridged bicyclic morpholine **4f** (52% yield) and dimethyl-substituted morpholine **4g** (86% yield). A wide range of piperazine-derived precursors bearing different functional groups were all effective, such as *N*-Boc **4h** (62% yield), *N*-Cbz **4i** (76% yield), *N*-Bz **4j** (69% yield), *N*-acrylamide **4k** (49% yield) and pyrimidine–

containing piperazine **4l** (47% yield). Seven-membered cyclic amine precursors, specifically azepane and *N*-Boc–protected 1,4-diazepane, successfully delivered **4m** and **4n** in 32% and 40% yields, respectively. Finally, acyclic hydroxylamine precursors were also found to be effective, as demonstrated in the successful installation of diethylamine (**4o**), and methylphenethylamine (**4p**). This protocol was even applicable for the direct formation of secondary amines (**4q–4r**), thus greatly expanding the types of *β*-fluoroalkylamines accessible using this method.

REGIOSELECTIVE 1,2 AMINOFLUORINATION OF 1,3-DIENES

We next investigated this copper-catalyzed aminofluorination of 1,3-dienes toward the formation of homoallylic *β*-fluoroamines, a class of highly valuable and synthetically flexible compounds (Table 2).[37-39] Such aminofluorination of 1,3-dienes comes with its own set of challenges and is even more complex than that of alkenes. First, the presence of two olefins may lead to the reactions occurring at two distinct sites. Second, the reaction may allow for either direct 1,2-addition or conjugated 1,4-addition products. Thus, the amino fluorination of 1,3-dienes could potentially lead to a series of isomeric products such as 1,2-addition products **6** and **6'** as well as 1,4-addition products **7** and **7'**. Our examination of reaction parameters toward the regioselective 1,2 aminofluorination suggested that IPrCuCl was a more effective catalyst in the reaction of 1,3-dienes (details in SI). Under the modified conditions, a series of 1-aryl-substiuted 1,3-dienes were studied. All selectively delivered 1,2-aminofluorination products, specifically homoallylic *β*-fluoroamines **6a**–**6f** in synthetically useful yields. The reactions of 1-alkyl-subsituted 1,3-dienes also favored 1,2-aminofluorination over 1,4-addition products. For example, the reaction of 1-hexyl-1,3-butadiene produced 1,2-product **6g** selectively, in a 7:1 ratio over 1,4-product **7g**. Similarly, the reaction of 1-cyclohexyl-1,3-butadiene favored **6h** over **7h** in an 8:1 ratio.

Most excitingly, this amino fluorination reaction of common, variously substituted 1,3-diene feedstocks readily delivered high-value homoallylic β-fluoroamines. For example, the reaction of the simplest 1,3-butadiene **5i** gave 1,2-product **6i** in 51% yield exclusively. The reaction of isoprene **5j** gave selectively 1,2-aminofluorination products, with **6j** and **6j'** formed in a ratio of 10:1, favoring the aminofluorination at the more branched site of terminal olefins. This site selectivity indicated the fluorination preferentially occurred at a more stabilized intermediate. The reactions of 2,3-dimethyl-1,3-butadiene **5k** successfully led to regioselective formation of 1,2-aminofluorination products such as 2-fluoropiperazine derivatives **6k** and **6l** using different alkylamine precursors. Finally, the reaction of cyclohexa-1,3-diene **5l** afforded *trans*-1,2-aminofluorination product **6m** in 45% yield, in a highly regio- and diastereoselective manner.

SYNTHETIC APPLICATIONS

To further illustrate the synthetic values of this aminofluorination method, we investigated the derivatizations of homoallylic β-fluoroamines (Figure 3, A). First, the homoallylic amines were successfully transformed into alkyl-substituted *β*-fluoroamines by Pd-catalyzed hydrogenation. Selected examples include 4-(2-fluoro-4-phenylbutyl)morpholine **3u** in 93% yield, *N*-Cbz (2-fluorobutyl)piperazine **7** in 96% yield, and *trans*-2-fluorocyclohexyl-

morpholine **8** in 92% yield. Such a route to β-fluoroalkylamines offers an effective entry to a wide range of β-fluoroalkylamines, alternative to the reactions using alkyl-substituted olefins. The ozonolysis of **6k** readily afforded ketone product **9** in 80% yield. Such a highly functionalized compound may find wide use in chemical synthesis. Furthermore, we have applied this aminofluorination system to the one-step preparation of structurally complex β-fluoroamine-containing bioactive compounds **10** (Figure 3, B). These successful derivatizations of important drugs such as ibuprofen (**10a**), fenofibrate (**10b**), indomethacin (**10c**), D-phenylalanine (**10d**), estrone (**10e**) and tryptamine derivative (**10f**) demonstrated high efficiency of this method and the remarkable tolerance of this catalytic method against different functional groups such as amide, ester, chloride, and ketone. Finally, we applied this method for a rapid synthesis of β-fluoropiperazine [F]-**YZ185** (**12**), as a novel analog of this class of sigma1 receptor ligands that have favorable features for anticocaine actions.[40] These representative examples highlight the advantages and potential application of this aminofluorination method in medicinal chemistry.

MECHANISTIC STUDIES

To shed light on the operating mechanism of this catalytic system, we investigated the reaction pathways that are engaged in this alkene aminofluorination reaction. Our previous studies have revealed a novel alkene activation mode initiated by copper-catalyzed amination using *O*-benzoyl-*N*-hydroxylamines, which involves the possible generation of nitrogen and carbon radical intermediates. To probe if a radical intermediate is involved in this aminofluorination reaction, control reaction using **1a** and **2a** was performed in the presence of butylated hydroxytoluene (BHT) as a radical scavenger (Figure 4, A). While only trace amount of the expected β-fluoroamine product **3a** was detected, BHT adduct **13a** was formed in 54% yield, strongly suggesting the generation of a stabilized carbon-centered benzylic radical intermediate under standard reaction conditions. Neither of the byproducts **13b** or **13c** was detected, suggesting no absence of long-lived nucleophilic nitrogen radicals. Furthermore, radical clock experiments using cyclopropylstyrenes **14a** and **14b** were performed (Figure 4, B). Aminofluorination of α-cyclopropylstyrene **14a** under the standard conditions produced only trace amount of aminofluorination product **15** and instead afforded the ring opening amination product **16** in 64% yield, which further implicates the involvement of a radical pathway and the presence of a benzylic radical. Such a species bearing the radical α to cyclopropane would be expected to undergo ring opening leading to a terminal radical and facile intramolecular trapping to produce **16**. In contrast, the reaction of β-*trans*-cyclopropylstyrene **14b** provided no desired product **17** nor any detectable ring-opening byproducts. This observation is consistent with the above hypothesis: the steric bulk of this 1,2-disubstituted alkene likely inhibits the reaction, even if the benzylic carbon radical is generated β to cyclopropane, no ring opening should be observed either.

Based on these experimental results and related studies,[30, 31, 41] the following reaction pathways are proposed (Figure 4, C). The reaction is initiated by copper-catalyzed N—O bond cleavage of *O*-benzoylhydroxylamines **2** in the presence of Et_3N•3HF, generating a protonated aminyl radical cation (**I**).[32, 33, 42-44] The subsequent electrophilic amination of carbon-carbon double bond would produce a carbon radical (**II**), which was supported by the

formation of **13a** and **16** (Figure 4, A and B). Under standard conditions, the resulting radical (**II**) would undergo copper-mediated fluorination. Et_3N•3HF was anticipated to have dual roles in this reaction, by contributing to the formation of aminyl radical cation as an acid source and enabling the effective fluorination step as a nucleophilic fluoride. Considering that the C—N bond formation the alkene electrophilic amination has always been facile and fast in our studies, the C—F bond formation step is likely the rate-determining step in this aminofluorination reaction. It remains inconclusive if the reaction engaged the formation of a possible aziridinium intermediate. Our future studies will be directed to elucidate the nature of the C—F bond formation step.

Standard conditions: olefin (2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), $Cu(HFacac)_2$ (5.0 mol %), Et_3N•3HF (10 equiv), DCE (1.0 mL), 80 °C, 2 h. Isolated yields shown.

CONCLUSIONS

In conclusion, we have developed an unprecedented copper-catalyzed aminofluorination of alkenes and 1,3-dienes using *N, N*-dialkylhydroxylamines and Et_3N•3HF as a direct entry to valuable (hetero)aryl, alkyl and homoallylic β-fluoroalkylamines. The method features high regioselectivity, mild conditions, good tolerance of diverse functional groups and a broad scope of commodity vinyl arenes and 1,3-dienes. Mechanistic experiments suggest a copper-mediated electrophilic amination of alkenes with the sequential formation of amine- and carbon-centered radical intermediates, which undergo nucleophilic fluorination to deliver the desired β-fluoroalkylamine products. The dual role of Et_3N•3HF as a fluoride source and an acid is significant and may direct future endeavors in this area of research. Synthetic applications of this method have been highlighted by its use for the rapid entry to β-fluoridated amine-containing pharmaceuticals, natural products, and bioactive compounds. We expect that this novel and practical procedure leading to highly valuable β-fluoroamines will find wide use in synthetic and medicinal chemistry community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We acknowledge financial support provided by Duke University and the National Institutes of Health (GM118786). We thank Dr. Peter Silinski (Duke University) for high-resolution mass spectrometry analysis.

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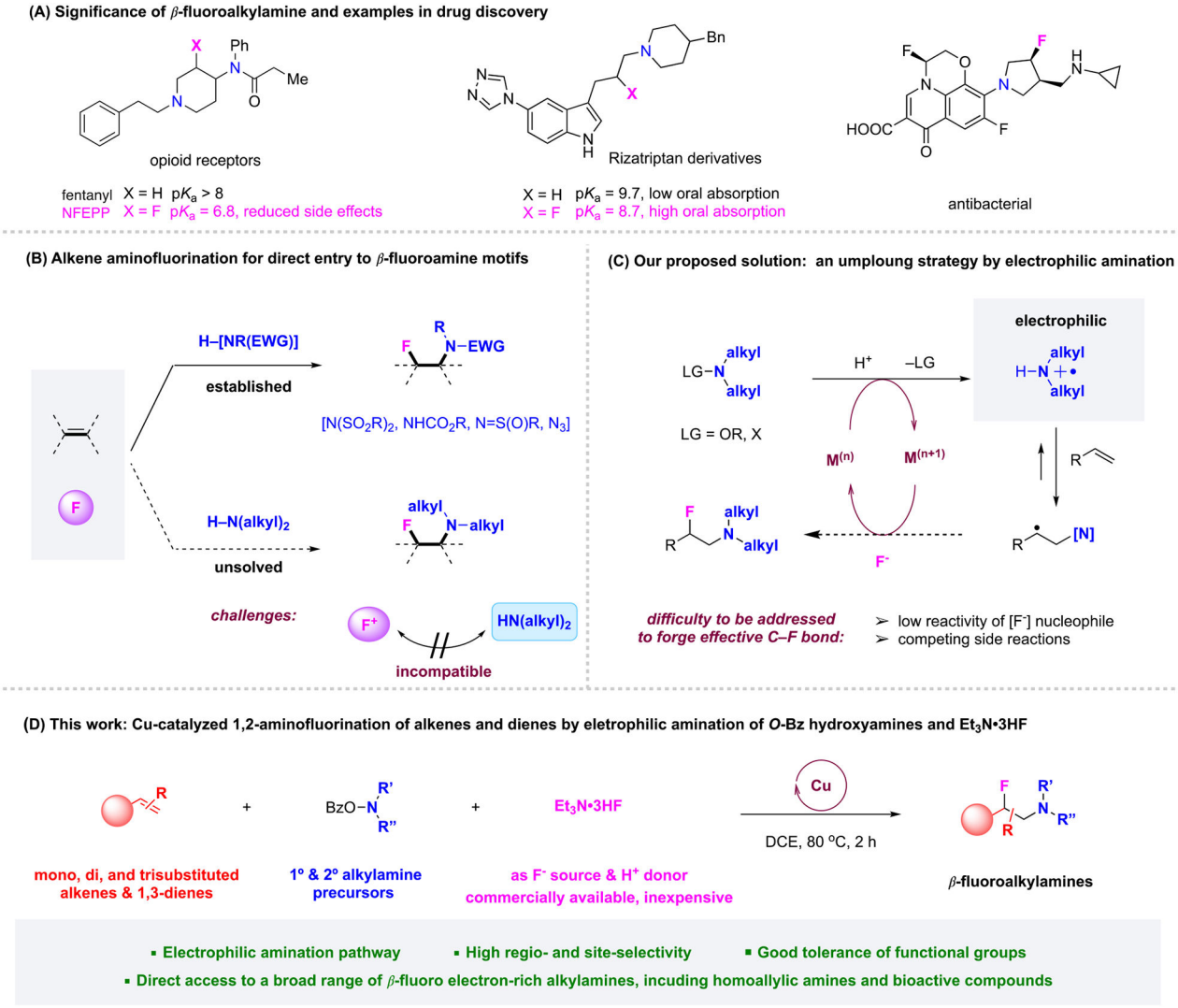


Figure 1. Alkene Aminofluorination for the Synthesis of β-Fluoroamines.

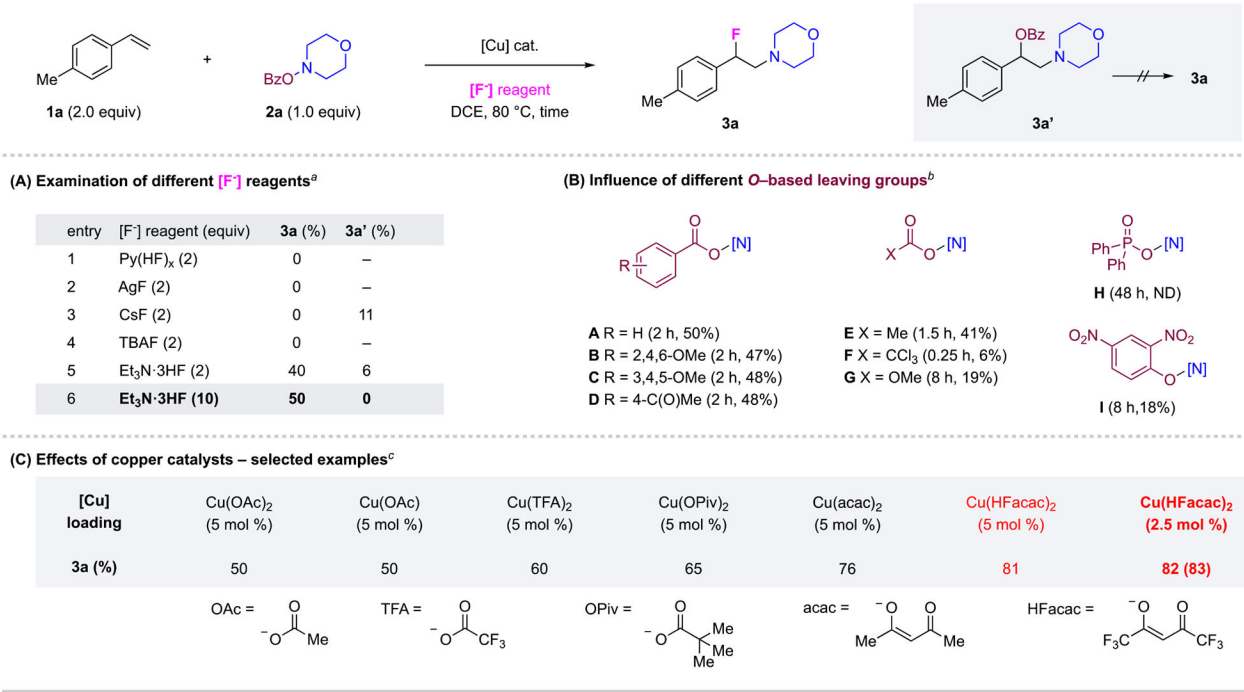


Figure 2. Condition Development for Alkene Aminofluorination Reaction.

Conditions: **1a** (2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), [F⁻] reagent, DCE (1.0 mL), 80 °C, 2 h, in 10-mL sealed FEP tube. Yields were determined by ^{1}H NMR of the crude mixture with dibromomethane as an internal standard. Isolated yields shown in parentheses. [a]$Cu(OAc)_2$ (10 mol %) used. [b]$Cu(OAc)_2$ (10 mol %) $Et_3N{\cdot}3HF$ (10 equiv), hydroxylamine derivative (1.0 equiv). [c]**2a** (1.0 equiv), $Et_3N{\cdot}3HF$ (10 equiv).

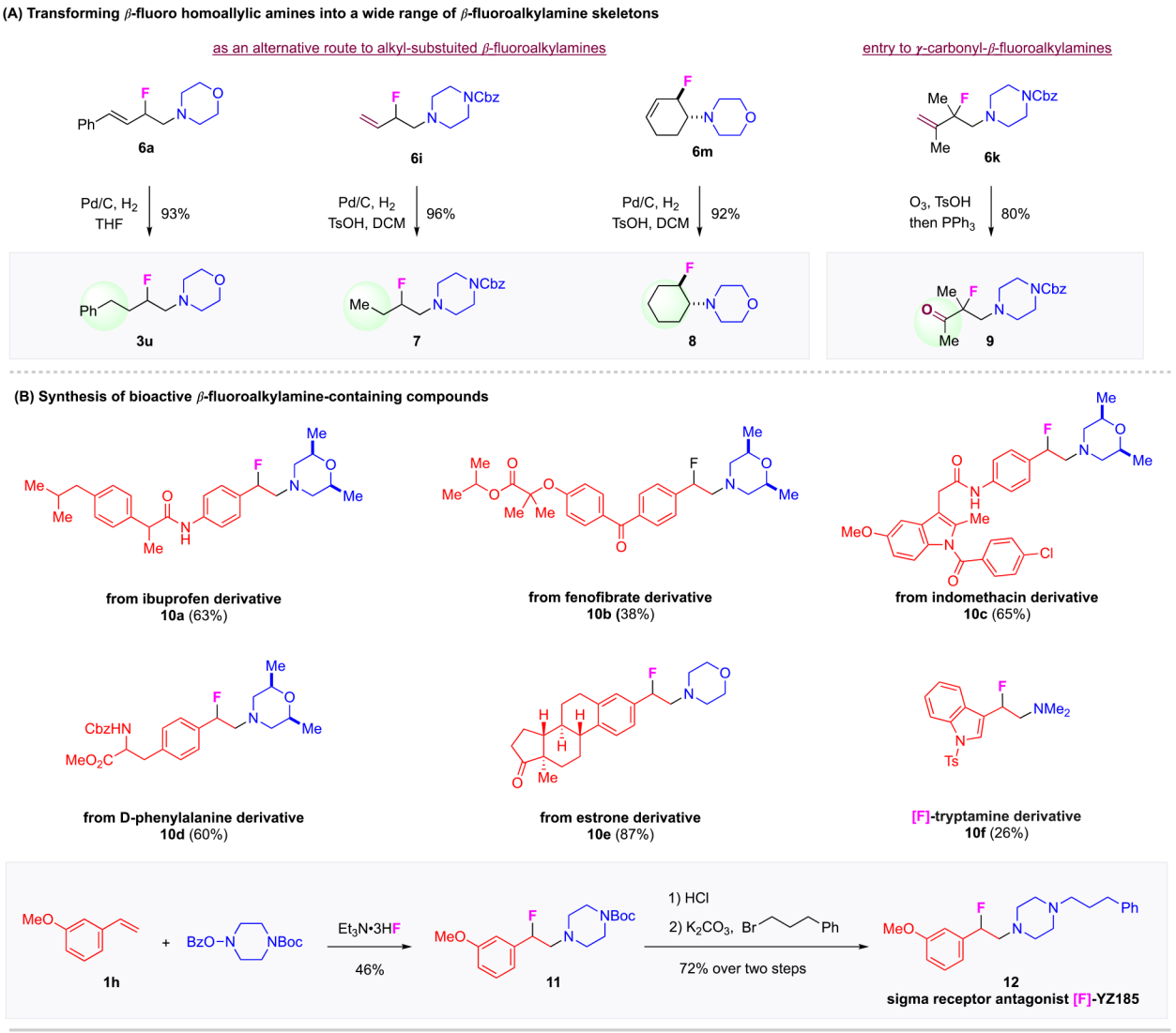


Figure 3. Application toward the Synthesis of β-Fluoroamine-Containing Bioactive Compounds.
(A) Derivatizations of homoallylic *β*-fluoroalkylamine products. (B) Synthesis of bioactive *β*-fluoroalkylamine-containing compounds.

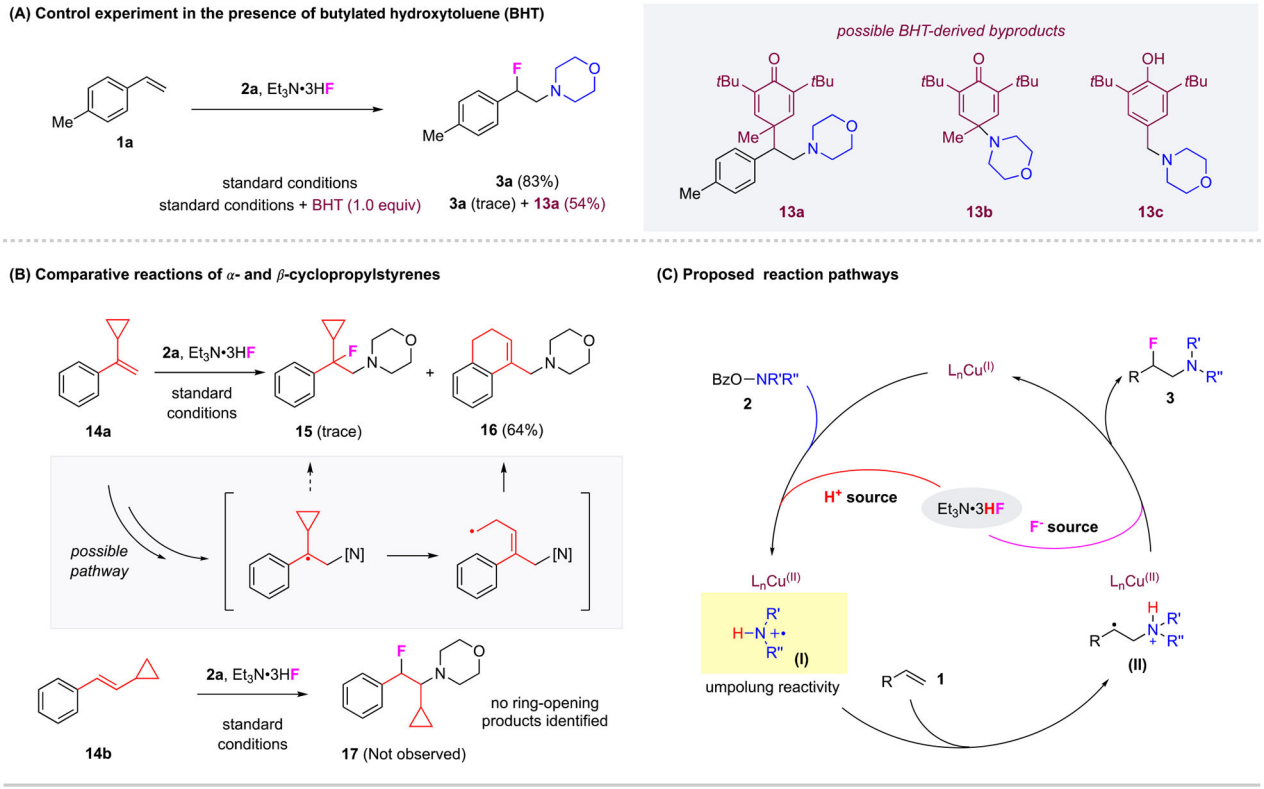
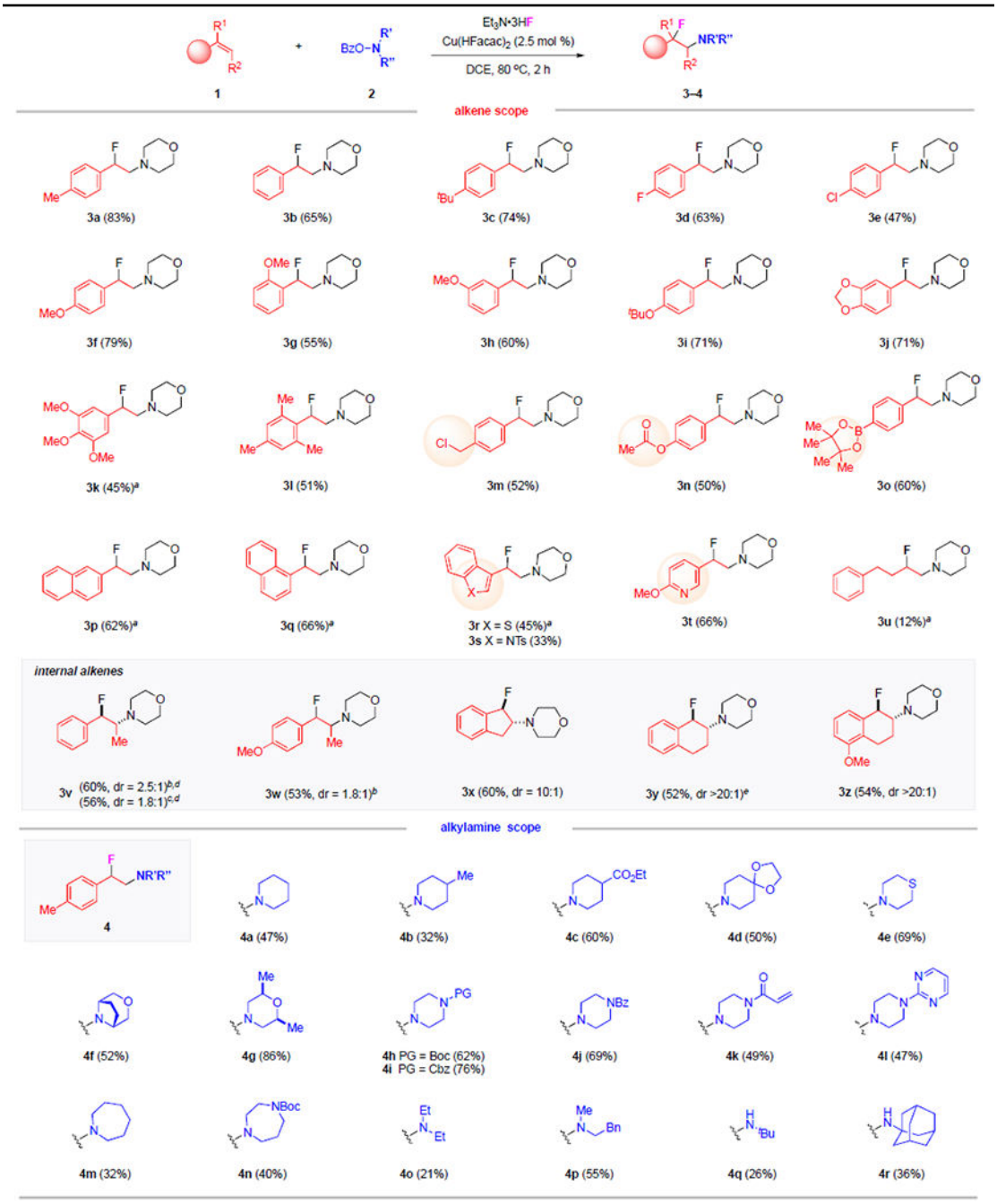


Figure 4. Mechanistic Studies on Cu-Catalyzed 1,2 Aminofluorination of Alkenes.

(A) Control experiment in the presence of butylated hydroxytoluene (BHT). (B) Comparative reactions of α- and β-cyclopropylstyrenes. (C) Proposed reaction pathways.

Table 1.

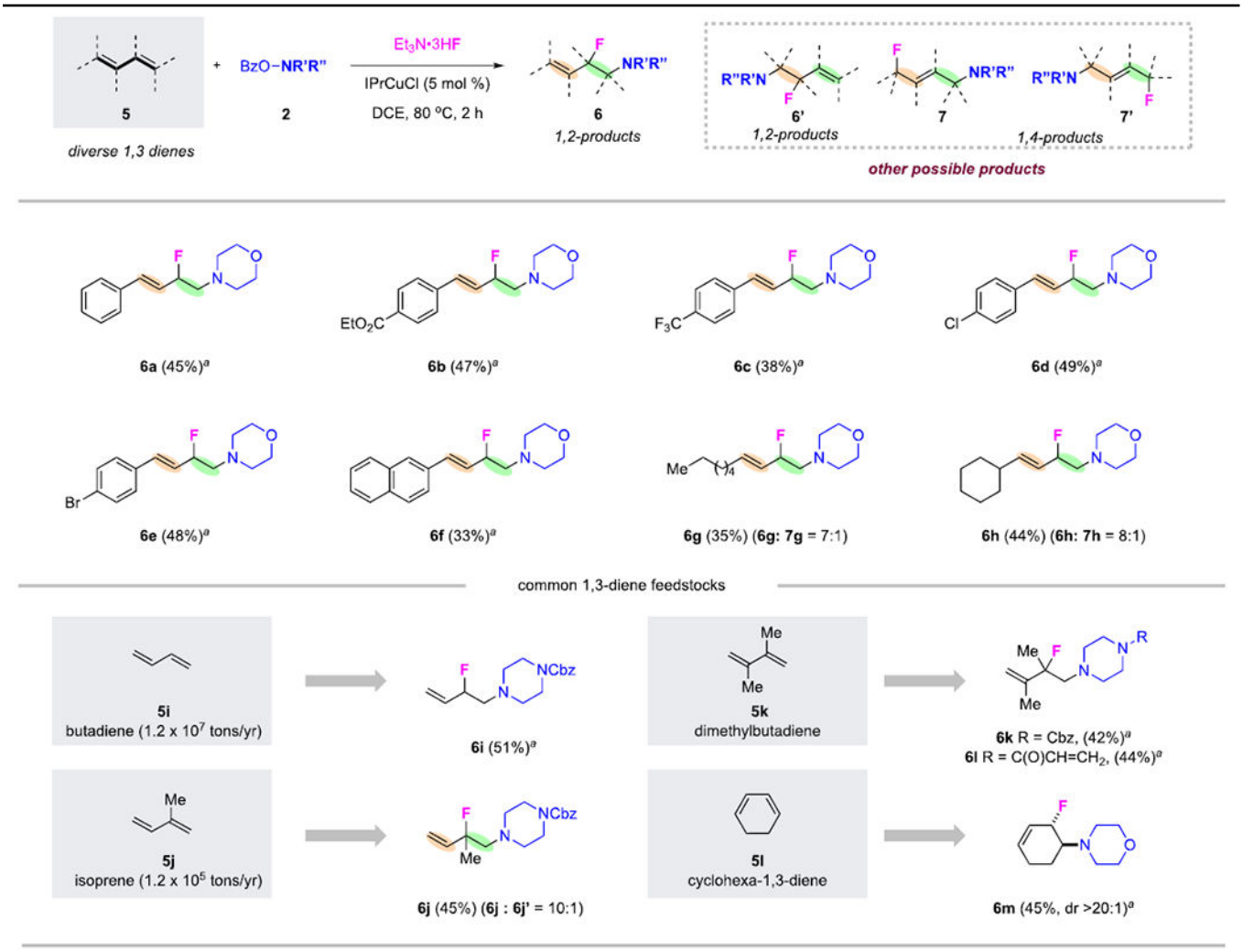
Intermolecular Aminofluorination Reactions – the Scope of Alkenes and Amines.



Reaction conditions: **1** (2.0 equiv), **2** (1.0 equiv), $Et_3N•3HF$ (10 equiv), $Cu(HFacac)_2$ (2.5 mol %), DCE (1.0 mL), 80 °C, 2 h. Isolated yields shown. dr determined by ^{1}H-NMR analysis of the crude mixtures. Major isomer shown. [a]IPrCuCl (5.0 mol %) used. [b]From *E*-alkene. [c]From *Z*-alkene. [d]Relative stereochemistry of the major diastereomer determined by X-ray analysis. [e]$CH_3(CH_2)_{10}C(O)O$–NR'R" used.

Table 2.

Copper-Catalyzed 1,2-Aminofluorination of 1,3-Dienes.



Reaction conditions: **5** (2.0 equiv), **2** (0.2 mmol, 1.0 equiv), $Et_3N•3HF$ (10 equiv), IPrCuCl (5.0 mol %), DCE (1.0 mL), 80 °C, 2 h. The major products shown. Isolated yields shown. Regioselectivity ratios (rr) were determined by ^{1}H-NMR analysis of the crude reaction mixtures. [a]rr > 20:1.