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Iron(II)-Catalyzed Intermolecular Aminofluorination of Unfunctionalized Olefins Using Fluoride Ion

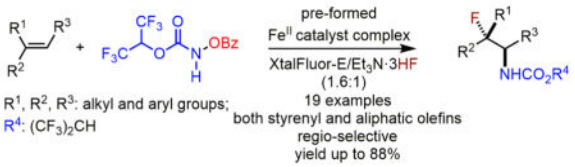
Deng-Fu Lu[†], **Cheng-Liang Zhu**[†], **Jeffrey D. Sears**, and **Hao Xu**[*]

Department of Chemistry, Georgia State University, 100 Piedmont Avenue SE, Atlanta, Georgia 30303, United States

Abstract

We herein report a new catalytic method for intermolecular olefin aminofluorination using earth-abundant iron catalysts and nucleophilic fluoride ion. This method tolerates a broad range of unfunctionalized olefins, especially nonstyrenyl olefins that are incompatible with existing olefin aminofluorination methods. This new iron-catalyzed process directly converts readily available olefins to internal vicinal fluoro carbamates with high regioselectivity (*N* vs *F*), many of which are difficult to prepare using known methods. Preliminary mechanistic studies demonstrate that it is possible to exert asymmetric induction using chiral iron catalysts and that both an iron-nitrenoid and carbocation species may be reactive intermediates.

Graphical Abstract



INTRODUCTION

Selective incorporation of fluorine into organic molecules is an emerging area with increasing importance in organic synthesis because fluorine atoms are present in numerous pharmaceuticals and biological probes.[1] In particular, intermolecular olefin functionalization via fluorine atom transfer represents a convenient approach to synthesize high-value building blocks with fluorine-containing stereogenic centers.[2] Among a variety of olefin fluorination

[*]Corresponding Author: hxu@gsu.edu.

[†]**Author Contributions**

D.-F.L. and C.-L.Z. contributed equally.

Notes

The authors declare no competing financial interest.

Supporting Information

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Experimental procedure, characterization data for all new compounds, selected NMR spectra and HPLC traces (PDF)

si_002.cif for compound **6** (CIF)

si_003.cif for Fe(**L1**)$_2$(BF$_4$)$_2$ (CIF)

si_004.cif for compound **7d** (CIF)

si_005.cif for compound **11a** (CIF)

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reactions, the *intermolecular amino-fluorination of unfunctionalized olefins* is of great value since it can directly convert simple olefins to vicinal fluoro primary amines which are important structural motifs in medicinal chemistry.[3] However, development of this catalytic reaction has been challenging; only a few methods were reported, and most of them are exclusively compatible with styrenyl olefins.[4]

Amid these discoveries, Stavber reported Ritter-type electrophilic olefin vicinal fluoro acetamidation in acetonitrile using electrophilic fluorination reagent Accufluor NFTh, through β-fluorocarbenium intermediates, to afford terminal fluorides; however, the substrate scope was predominantly limited to styrenyl olefins.[4a] Liu reported palladium-catalyzed styrene aminofluorination using electrophilic NFSI, which affords terminal sulfonamido fluorides;[4b] the same group later documented a related styrene aminofluorination using AgF that provides internal sulfonamido fluorides.[4e]

The existing intermolecular olefin aminofluorination methods are mechanistically illuminating; however, there still exist significant gaps for this important transformation. First, there has yet to be developed a method for catalytic amino-fluorination of *a broad range of unf unctionalized olef ins* (especially for nonstyrenyl olefins). Next, the feasibility of asymmetric catalysis for intermolecular aminofluorination of unfunctionalized olefins has not yet been demonstrated.[5] Additionally, the use of earth-abundant iron catalysts to promote olefin aminofluorination with simple nucleophilic fluoride ion is desirable,[6] especially considering potential applications in ^{18}F PET imaging; however, *iron-catalyzed intermolecular olefin fluorination using nucleophilic fluoride remains unreported*,[7] presumably because of the high BDE of the Fe–F bond,[8] the low solubility of iron fluoride species, and low nucleophilicity of solvated fluoride ion in organic solvents.[9]

Herein, we report an iron-catalyzed intermolecular amino-fluorination method for a broad range of unfunctionalized olefins, including nonstyrenyl olefins, using fluoride ion (Scheme 1). This new reaction readily affords a variety of synthetically valuable vicinal fluoro carbamates with high regioselectivity (*N* vs *F*), many of which are difficult to prepare using existing methods.[10] We further demonstrate that it is possible to modulate the enantioselectivity for aminofluorination of cyclic olefins. Additionally, preliminary mechanistic studies suggest a possible new olefin aminofluorination pathway in which both an iron-nitrenoid and carbocation species may be involved in a stepwise nitrogen and fluorine atom transfer.

RESULTS AND DISCUSSION

We previously reported an iron-catalyzed method for *intra-molecular* olefin aminofluorination using fluoride ion in which iron(II)–bidentate ligand complexes catalyze the reaction in the presence of $Et_3N{\cdot}3HF$ (Scheme 2A);[11] however, this type of catalyst was ineffective to catalyze the *intermolecular* olefin aminofluorination because of lack of reactivity (Scheme 2B). We also reported an iron-catalyzed method for *intermolecular olefin aminohydroxylation* using iron(II)–tridentate ligand complexes;[12] however, these catalysts were unable to promote the *intermolecular olefin aminofluorination* in the presence of $Et_3N{\cdot}3HF$, possibly due to catalyst deactivation (Scheme 2B). We therefore explored a range

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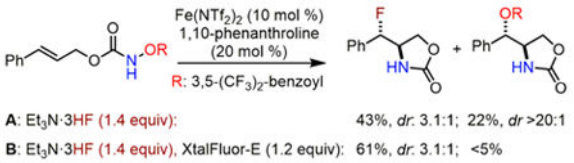
of catalysts, oxidants, and fluorination reagents to search for a *stable yet reactive* catalyst in the presence of the nucleophilic fluoride ion.

To determine the possible cause of the aforementioned catalyst deactivation (Scheme 2B), we exposed an *in situ* generated $Fe(BF_4)_2$–**L1** catalyst (1:1 ratio), previously discovered for styrene aminohydroxylation, to an intra-molecular aminofluorination condition in the absence of any olefin or oxidant (Scheme 3). Insoluble FeF_2 and a soluble iron complex were obtained, and X-ray crystallographic analysis revealed its structure as Fe(**L1**)$_2$(BF_4)$_2$, which, surprisingly, is inactive for styrene aminohydroxylation.[13] This result suggests that fluoride species may disrupt the $Fe(BF_4)_2$–**L1** complex through iron sequestering and therefore lead to the inactive Fe(**L1**)$_2$(BF_4)$_2$ catalyst formation.

During the discovery of the aforementioned iron-catalyzed intramolecular olefin aminofluorination, we identified that electrophilic XtalFluor-E[14] effectively suppresses the competing olefin aminohydroxylation, presumably by sequestering the benzoate generated during the N–O bond cleavage (eq 1).[11,14]



(1)

We also noted, through NMR titration experiments, that XtalFluor-E and $Et_3N{\cdot}3HF$[15] may form dynamic complexes (Scheme 4),[16] which could attenuate the concentration of $Et_3N{\cdot}3HF$ and therefore significantly slow down the putative fluoride-induced catalyst deactivation.

To test this hypothesis, we selected styrene **1** as a model substrate for catalyst discovery (Table 1). We first observed that the $Fe(NTf_2)_2$–**L1** complex, a catalyst for styrene amino-oxygenation, led to inefficient aminofluorination when a 1:1 mixture of XtalFluor-E and $Et_3N{\cdot}3HF$ was used: vicinal amino fluoride **3** was obtained in a low yield (16%) together with the amino-oxygenation product **4** (entry 1). Notably, there was no reaction in the absence of an iron catalyst; both **1** and **2a** were stable toward XtalFluor-E and $Et_3N{\cdot}3HF$, and they were fully recovered (entry 2).

We also observed a higher yield of **3** when the XtalFluor-E/$Et_3N{\cdot}3HF$ ratio was increased to 1.6:1 (entry 3, XtalFluor-E (2.5 equiv), $Et_3N{\cdot}3HF$ (1.5 equiv), 42% yield). Suspecting that an extra equivalent of XtalFluor-E may sequester the carboxylate generated during the N–O bond cleavage, we replaced **2a** with **2b**, from which we expected a more nucleophilic benzoate to be generated. A similar yield of **3** and a better mass balance were observed (entry 4). Interestingly, a 2:1 mixture of XtalFluor-E/$Et_3N{\cdot}3HF$ resulted in a decreased yield of **3** and isolation of imidazoline **5**, presumably through MeCN (cosolvent) incorporation

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(entry 5). Notably, no desired product was observed in the absence of $Et_3N{\cdot}3HF$, and only **5** was isolated (entry 6).

In order to attenuate the neighboring carbamate group's participation, we switched **2b** to more electrophilic **2c** and **2d** and observed further improved yield of **3** (entries 7–8, 46–73% yield). Furthermore, an excess amount of both XtalFluor-E and $Et_3N{\cdot}3HF$ is beneficial to the yield of **3** (entry 9, 81% yield), and the $Fe(NTf_2)$–**L2** complex provides essentially the same yield (entry 10, 78% yield). To our surprise, Fe(**L1**)-$(MeCN)(H_2O)_2(BF_4)_2$ (**6**), a crystalline solid that was easily prepared and handled outside of a glovebox (Figure 1), was found to effectively catalyze styrene aminofluorination in the absence of the MeCN cosolvent; **3** was isolated in an excellent yield without using an excess amount of fluorination reagent (entry 11, 88%).[13]

To better understand the structure–reactivity relationship of fluoride donors, we explored a range of variations using other nucleophilic fluorination reagents under the optimized conditions (Table 2). First, replacements of $Et_3N{\cdot}3HF$ with $Et_3N{\cdot}HF$, $Et_3N{\cdot}2HF$, TBAF·$(^tBuOH)_4$, KF, or AgF all lead to unproductive decomposition of **2d** (entry 1).[17] Next, replacement of XtalFluor-E with XtalFluor-M also affords **3d**, albeit in a lower yield (entry 2, 65% yield). Furthermore, using benzoyl fluoride instead of $Et_3N{\cdot}3HF$/XtalFluor-E does not afford the desired product **3**, but rather leads to benzoylation of **2d** (entry 3). Furthermore, using DFI,[18] PhenoFluor,[19] or DAST,[20] reagents that can presumably sequester benzoates, leads to unproductive decomposition of **2d** (entries 4–5). Surprisingly, the DAST/XtalFluor-E (1:1) combination can lead to full conversion of **1** and generation of amino fluoride **3d** (entry 6, 51% yield). This result corroborates the proposal that $Et_3N{\cdot}3HF$ and XtalFluor-E may form dynamic complexes, which are compatible with the iron catalyst (Scheme 4).

Upon discovering the optimal catalytic conditions, we explored the substrate scope of this new reaction (Table 3). First, a range of styrenes with various electronic properties are compatible with this method, and they were converted to internal amino fluorides with excellent yields (entries 1a–1d). Additionally, ene-yne and α-methylstyrene are both excellent substrates (entries 2–3).

Next, *we evaluated olefins that are incompatible with existing aminofluorination methods*. An allyl silane with a labile C–Si bond in the presence of fluoride ion was converted to an internal amino fluoride, which has a nitrogen, fluorine, and silicon-based triad with excellent yield and regioselectivity (entry 4, 82% yield). A silyl dienol and an ethyl dienoate, both with labile functional groups, were also tolerated by this method to produce amino allylic fluorides in reasonable yields (entries 5–6). Isoprene aminofluorination provided a pair of vicinal amino allylic fluorides with an excellent yield and good regioselectivity (entry 7, 84% yield). Furthermore, a linear aliphatic diene was converted to both 1,2- and 1,4-amino fluorides with excellent combined yield (entry 8, 91% yield).

We subsequently explored indene aminofluorination using the $Fe(NTf_2)_2$–**L1** complex: an *anti*-2-amino fluoride was isolated with excellent regioselectivity and significant diastereoselectivity (entry 9, 72% yield, dr: 6.2:1).[23] Moreover, we evaluated isolated

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olefins, including 1,1-disubstituted and monosubstituted olefins, both of which are significantly less reactive. With increased catalyst loading and the amount of fluorination reagents, both of them were converted to internal amino fluorides with reasonable yields and high regioselectivity (entries 10–11, 62–71% yield). *Notably, this new method enables the synthesis of a range of structurally diverse vicinal amino fluorides for the first time (described in entries 4, 5, 7, 10, and 11)*.

The furnished vicinal fluoro carbamates, both from styrenyl and aliphatic olefins, such as **7** and **9**, can be easily derivatized to *N*-Boc protected vicinal fluoro amines **8** and **10** in excellent yields under mild conditions (Scheme 5).[13]

With the success of this aminofluorination method for simple unfunctionalized olefins, we further explored this new reaction with complex olefins, including myrcene which contains both a trisubstituted olefin and a conjugated diene, and (−)-β-pinene (Scheme 6). The aminofluorination of myrcene readily affords both a standard 1,2-addition product **11b** and a 1,6-addition product **11a** presumably through cyclization. We also note that the nitrogen atom was selectively transferred to the same terminal positions in both **11a** and **11b**. To our surprise, the aminofluorination of (−)-β-pinene does not afford any 1,2-addition product, but rather the same 1,6-addition product **11a** presumably through rearrangement. Notably, complete stereochemistry retention is observed in this aminofluorination–rearrangement cascade.[24]

Fluorinated amphetamines are of great interest to biological studies of the central nervous system; therefore, we evaluated the aminofluorination of *trans*-β-methylstyrene (Scheme 7).[25] Interestingly, although the $Fe(BF_4)_2$–**L1** complex **6** promotes undesirable C–H abstraction, a less sterically hindered $Fe(NTf_2)_2$–**L2** complex catalyzes efficient aminofluorination to afford **12** (Scheme 7, 72% yield, dr: 2.0:1).[13]

In order to demonstrate the potential practicality of this reaction, we explored the aminofluorination of indene and isoprene on a large scale (Scheme 8). To our pleasure, both catalytic reactions can be scaled up to gram scale with consistent yield and regio- and stereoselectivity.[13]

The catalytic enantioselective aminofluorination of unfunctionalized olefins has been an unsolved synthetic challenge;[26] therefore, we explored the feasibility of achieving asymmetric induction using chiral iron catalysts. As a first step, we studied asymmetric indene aminofluorination as a proof of concept, which may provide valuable mechanistic insights (Table 4). The $Fe(NTf_2)_2$–chiral ligand **L3** complex catalyzes indene aminofluorination with **2d** and affords *anti*-2-amino fluoride **7d** with significant ee (entry 1, 60% ee). Although less sterically hindered acyloxyl carbamates (**2b** and **2c**) lead to further increased ee for indene aminofluorination, both reactions evidently suffer from lower reactivity (entries 2–3, 78–83% ee). In order to achieve enhanced reactivity, the benzoyl activating group in **2c** was switched to 3,5-bis(trifluoromethyl)-benzoyl group in **2e**. To our surprise, a dramatically decreased ee was observed (entry 4, 55% ee). Fortunately, indene aminofluorination with acyloxyl carbamate **2f**, which has a 2,4-dichloro-benzoyl activating group, provides **7** with a synthetically useful yield and high ee (entry 5, 59% yield, 84% ee).

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Other chiral ligands, including tridentate **L4** and **L5**, were also evaluated, and they all provided inferior results.

These results also provide valuable mechanistic insight. The acyloxyl moiety on **2** proves crucial for stereochemical communication in the iron-catalyzed indene aminofluorination (Table 4, entries 3–5). This observation suggests that the benzoate generated during N–O bond cleavage may be involved in the ee-determining step. Additionally, since the same ee was observed for both diastereomers of **7**, it is likely that the C–N bond forming step is ee-determining.

In order to formulate a mechanistic model, we carried out several control experiments to gain more insight into both the C–N and C–F bond forming steps (Scheme 9). First, two analogues of **2** in which the *N*–H moiety was replaced with either the *N*–Me or *N*–Ac groups were subjected to standard reaction conditions (Scheme 9, eq 2). Neither was reactive toward the aminofluorination, which suggests that the N–H moiety in **2** is critical for its activation.

Next, the aminofluorination of a cyclopropyl-substituted olefin **15** afforded only the ring-opening products **16** and **17** (Scheme 9, eq 3). This result, together with the observed 1,6-myrcene aminofluorination, suggests that the reaction may proceed through a stepwise process and that a carbo-radical species may be an intermediate. To obtain more mechanistic details beyond the C–N bond forming step, we further evaluated a 1,1-disubstituted olefin **18** and observed both 1,2-amino fluoride **19** and 1,3-aminofluoride **20** which is presumably obtained through 1,2-hydride shift from a carbocation (Scheme 9, eq 4). This result suggests that a carbocation may also be involved in the reaction pathway.

Furthermore, benzoylated morpholine **21** was identified as a side product in styrene aminofluorination using $Et_3N{\cdot}3HF$/ XtalFluor-M (Scheme 9, eq 5). We suspected that **21** might be derived from the interaction between XtalFluor-M and the benzoic acid that was generated during the iron-catalyzed N–O bond cleavage; therefore, a control experiment between benzoic acid and XtalFluor-M was conducted, from which **21** was indeed isolated (Scheme 9, eq 6). These results suggest that XtalFluor-E or XtalFluor-M sequesters benzoic acids to promote efficient fluorine atom transfer.

On the basis of a range of mechanistic evidence presented in Scheme 9, a mechanistic working hypothesis for the iron-catalyzed olefin aminofluorination is proposed in Scheme 10. First, the iron catalyst may reductively cleave the N–O bond in **2**, which can possibly be converted to an iron-nitrenoid **A**. The iron-nitrenoid may initiate a radical addition with olefin **1** to afford a carbo-radical species **B**. Subsequently, the high-valent iron intermediate may further oxidize the radical, presumably through single electron transfer (SET),[27] to generate a carbocation **C1**. When the concentration of a suitable fluoride donor is low, **C1** may be efficiently intercepted by the neighboring carbamate group to afford amino-oxygenation product **4**.

However, in the presence of a suitable nucleophilic fluoride and benzoate sequestering reagent (e.g., $Et_3N{\cdot}3HF$/XtalFluor-E), carbocation **C1** may be rapidly converted to **C2**,

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which can be captured and converted to amino fluoride **3**; therefore, the aminofluorination pathway will override the competing amino-oxygenation pathway. Since oxazoline **4** may also be converted to carbocation **C1** under reaction conditions which are strongly Lewis acidic, it is possible that this additional pathway may also operate, for a certain type of substrates, to afford the olefin aminofluorination product **3**.

CONCLUSION

In conclusion, we reported a catalytic method for intermolecular olefin aminofluorination using earth-abundant iron catalysts and nucleophilic fluoride ion. This method tolerates a broad range of unfunctionalized olefins, including nonstyrenyl olefins that are incompatible with existing aminofluorination methods. It also readily affords a variety of synthetically valuable vicinal fluoro carbamates with high regioselectivity. Notably, many of them are difficult to prepare using existing methods. We systematically described the catalytic discovery, structure–reactivity relationship studies of fluoride donors, substrate scope and limitation of this method, derivatization of vicinal fluoro carbamates under mild conditions, practical procedures for gram-scale olefin aminofluorination, chiral catalyst discovery for asymmetric olefin aminofluorination, and preliminary mechanistic studies. These studies demonstrate that it is feasible for asymmetric induction using chiral iron catalysts for aminofluorination of unfunctionalized olefins, in which both an iron nitrenoid and a carbocation species may be possible reactive intermediates. Our current efforts focus on both mechanistic understanding and synthetic applications of this new reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. An additional amount of XtalFluor-E/Et_3N·3HF was used to convert oxazolines to corresponding amino fluorides.
23. For a diastereoselective indene aminofluorination to afford 1-amino fluoride, which is the regioisomer of **7**, see ref 4e.
24. The ee for (−)-β-pinene is 92%, and the ee for **11a** is 91%. For experimental details, see the Supporting Information.
25. For a selected example of fluorinated amphetamine synthesis, see: Cresswell AJ, Davies SG, Lee JA, Roberts PM, Russell AJ, Thomson JE, Tyte MJ. Org Lett. 2010; 12:2936. [PubMed: 20509635]
26. For iron-catalyzed asymmetric intramolecular olefin amino-fluorination, see ref 11. For a recent review of asymmetric fluorocyclization, see: Wolstenhulme JR, Gouverneur V. Acc Chem Res. 2014; 47:3560. [PubMed: 25379791] For other selected examples of asymmetric fluorination, see: Beeson TD, MacMillan DWC. J Am Chem Soc. 2005; 127:8826. [PubMed: 15954790] Kalow JA, Doyle AG. J Am Chem Soc. 2010; 132:3268. [PubMed: 20163118] Rauniyar V, Lackner AD, Hamilton GL, Toste FD. Science. 2011; 334:1681. [PubMed: 22194571] For asymmetric olefin difluroination, see ref 2b–d. For asymmetric fluoro aminoxylation of enals using organocatalysis, see ref 5. For a recent review of asymmetric olefin aminohalogenation, see: Chemler SR, Bovino MT. ACS Catal. 2013; 3:1076. [PubMed: 23828735]
27. (a) Kharasch MS, Sosnovsky G. J Am Chem Soc. 1958; 80:756.(b) Kochi JK. Science. 1967; 155:415. [PubMed: 17737550]

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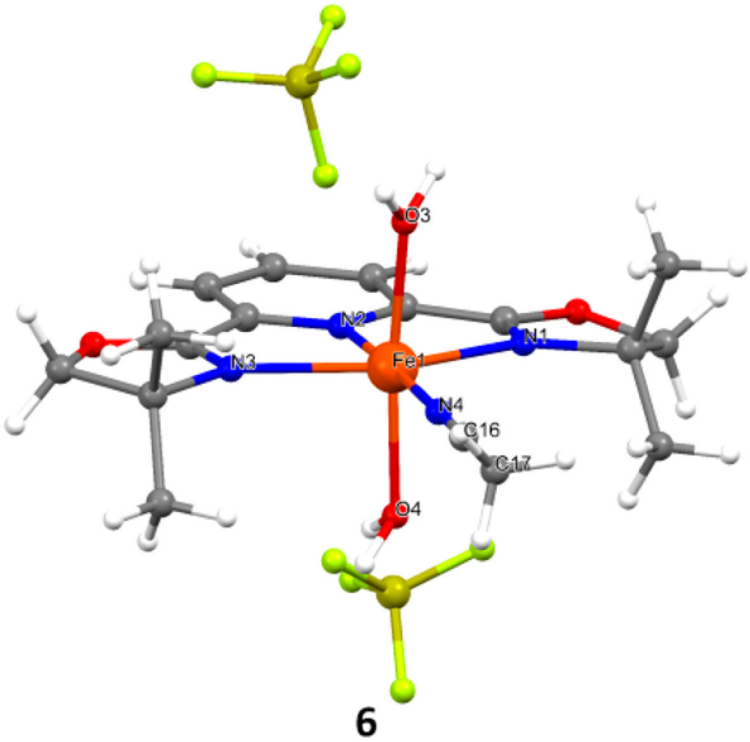
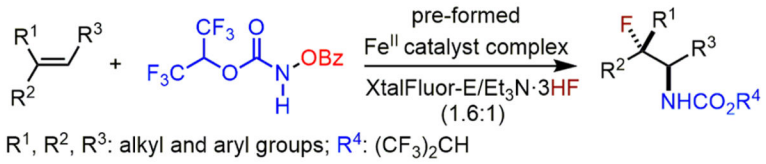


Figure 1.
Crystal structure of Fe(**L1**)(MeCN)$(H_2O)_2(BF_4)_2$ (**6**).



Scheme 1.

Iron-Catalyzed Intermolecular Olefin Aminofluorination Using Fluoride Ion

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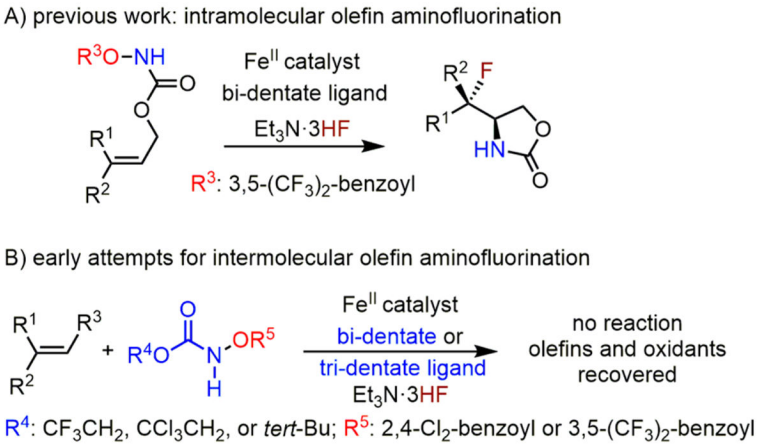
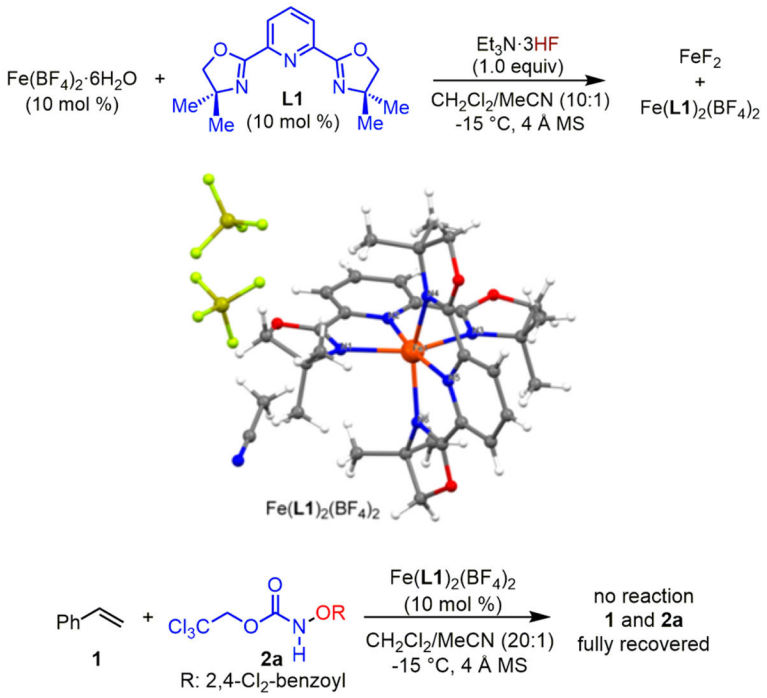


Scheme 2.

Iron-Catalyzed Intramolecular Olefin Aminofluorination and Early Attempts for Intermolecular Olefin Aminofluorination



Scheme 3.

Experiments To Explore the Putative Fluoride-Induced Catalyst Deactivation

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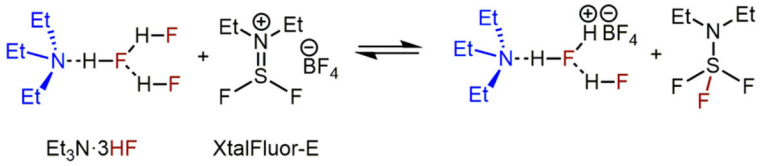

Scheme 4.

Proposed Complex Formation from $Et_3N{\cdot}3HF$ and XtalFluor-E

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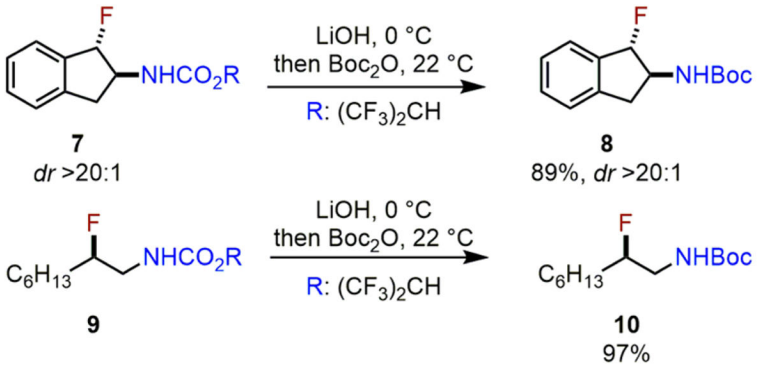
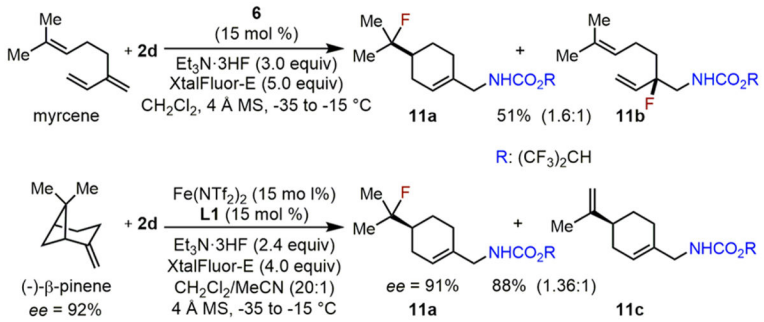


Scheme 5.

Derivatization of Olefin Aminofluorination Products to *N*-Boc-Protected Vicinal Fluoro Amines



Scheme 6.

Iron-Catalyzed Aminofluorination of Myrence and (−)-*β*-Pinene

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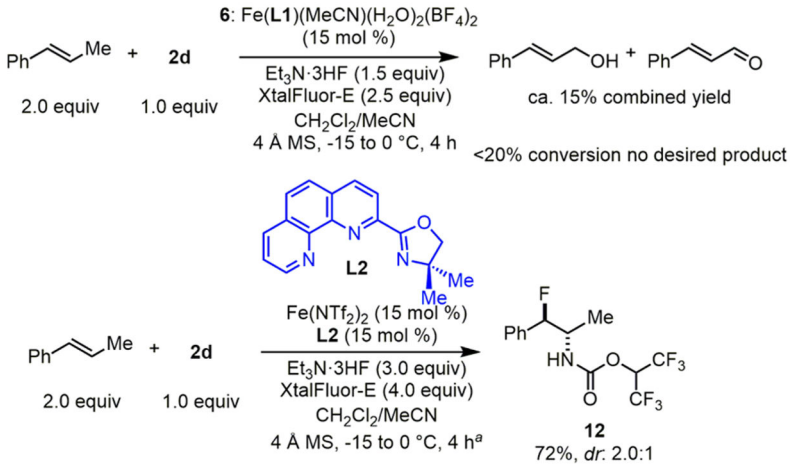

Scheme 7. Iron-Catalyzed Aminofluorination of *trans*-*β*-Methyl-styrene

[a]Reaction condition: $Fe(NTf_2)_2$ (15 mol %), L2 (15 mol %), XtalFluor-E (2.5 equiv)/ $Et_3N{\cdot}3HF$ (1.5 equiv), 4 Å MS, CH_2Cl_2/MeCN, −15 °C, 1 h; then, another portion of XtalFluor-E (1.5 equiv)/$Et_3N{\cdot}3HF$ (1.5 equiv), 0 °C, 3 h.

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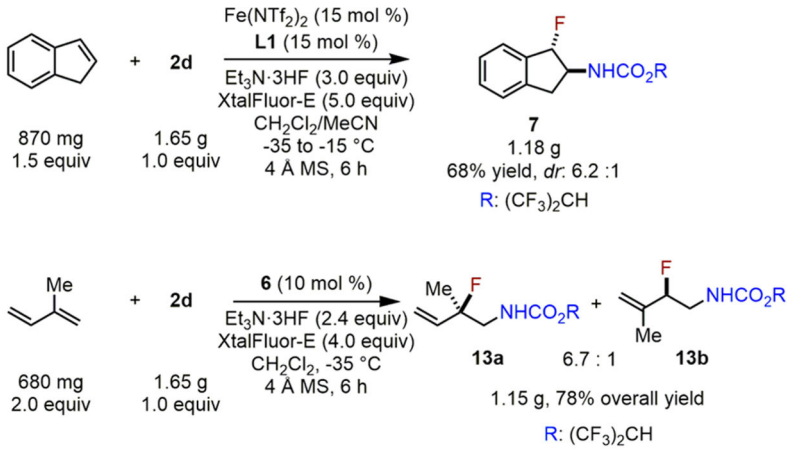

Scheme 8.

Iron-Catalyzed Gram-Scale Aminofluorination of Indene and Isoprene

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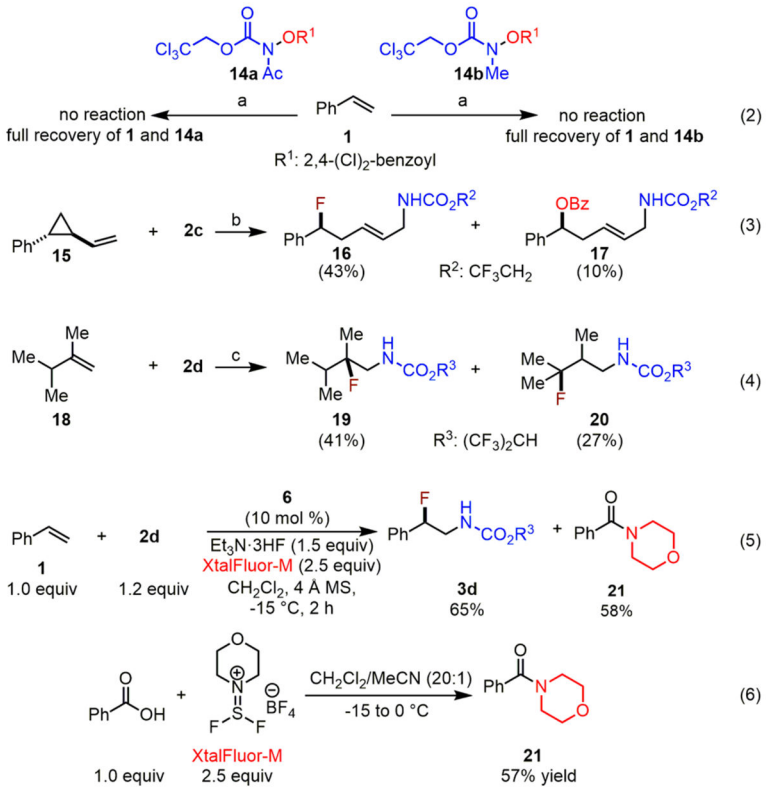

Scheme 9. Control Experiments To Probe for Mechanistic Insight

[a]6 (15 mol %), XtalFluor-E (2.5 equiv)/$Et_3N{\cdot}3HF$ (1.5 equiv), −15°C, CH_2Cl_2. [b]**6** (15 mol %), XtalFluor-E (4.0 equiv)/$Et_3N{\cdot}3HF$ (2.4 equiv), −40 °C, CH_2Cl_2. [c]**6** (15 mol %), XtalFluor-E (3.0 equiv)/$Et_3N{\cdot}3HF$ (1.8 equiv), −35 to 0 °C, CH_2Cl_2. R^1: 2,4-Cl_2-benzoyl, R^2: CF_3CH_2, R^3: $(CF_3)_2CH$.

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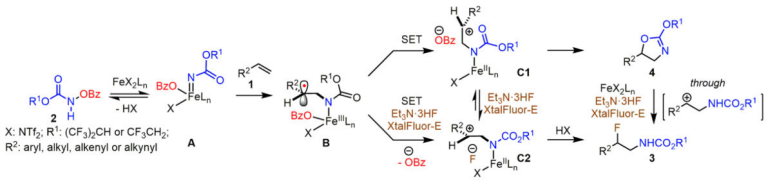

Scheme 10.

Mechanistic Working Hypothesis of the Iron-Catalyzed Intermolecular Olefin Aminofluorination Using Fluoride Ion

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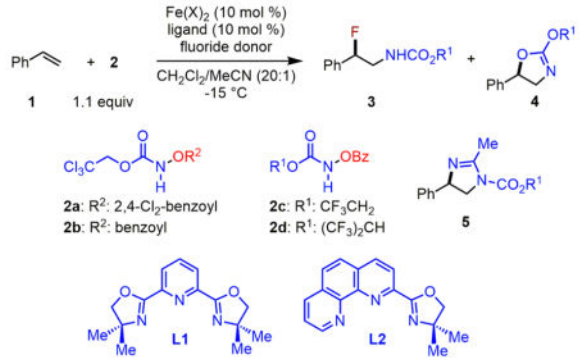
Table 1

Catalyst Discovery for the Intermolecular Olefin Aminofluorination



entry[a]	$Fe(X)_2$	ligand	2	$Et_3N{\cdot}3HF$ (equiv)	XtalFluor-E (equiv)	yield (3)[b]	yield (4)[b]
1	$Fe(NTf_2)_2$	**L1**	**2a**	1.5	1.5	16%	30%
2[c]	none	none	**2a**	1.5	1.5	NA	NA
3	$Fe(NTf_2)_2$	**L1**	**2a**	1.5	2.5	42%	17%
4	$Fe(NTf_2)_2$	**L1**	**2b**	1.5	2.5	45%	23%
5[d]	$Fe(NTf_2)_2$	**L1**	**2b**	1.5	3.0	23%	52%
6[e]	$Fe(NTf_2)_2$	**L1**	**2b**	none	1.5	NA	NA
7[d]	$Fe(NTf_2)_2$	**L1**	**2c**	1.5	2.5	46%	44%
8[d]	$Fe(NTf_2)_2$	**L1**	**2d**	1.5	2.5	73%	<5%
9[d]	$Fe(NTf_2)_2$	**L1**	**2d**	2.4	4.0	81%	<5%
10[d]	$Fe(NTf_2)_2$	**L2**	**2d**	2.4	4.0	78%	<5%
11[f]	6: $Fe(L1)(BF_4)_2(MeCN)(H_2O)_2$	none	**2d**	1.5	2.5	88%	<5%

[a]Reactions were carried out under N_2 at −15 °C in 2 h, and 4 Å activated molecular sieves (powder) were used to remove deleterious moisture, unless stated otherwise. The reaction was quenched with saturated $NaHCO_3$ solution.

[b]Isolated yield.

[c]No reaction; **1** and **2a** were recovered.

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[d]The yield of **5** is 8–12%.

[e]No desired product observed, and **5** (42%) was isolated.

[f]Preformed complex **6** was used as the catalyst in CH_2Cl_2 in the absence of MeCN; −15 °C, 2 h; the yield of **5** is less than 5%.

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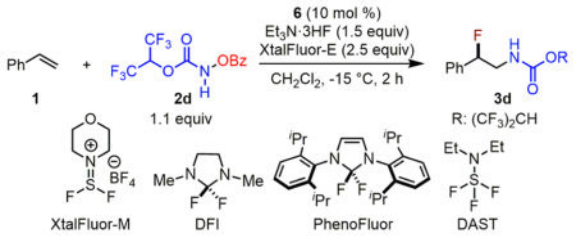
Table 2

Structure–Reactivity Relationship Studies of Nucleophilic Fluorination Reagents



entry[a]	variation from the std conditions	observations
1	replace $Et_3N{\cdot}3HF$ with $Et_3N{\cdot}HF$, $Et_3N{\cdot}2HF$, TBAF(^{t}BuOH)$_4$, or AgF	decomposition of **2d**, no desired product
2	replace XtalFluor-E with XtalFluor-M	**3d** (65%) with full conversion
3	replace $Et_3N{\cdot}3HF$/XtalFluor-E with benzoyl fluoride	**3d** (<5%) with 66% conversion[b]
4	replace $Et_3N{\cdot}3HF$/XtalFluor-E with DFI or PhenoFluor	decomposition of **2d**, no desired product
5	replace $Et_3N{\cdot}3HF$/XtalFluor-E with DAST	decomposition of **2d**, no desired product
6	replace $Et_3N{\cdot}3HF$/XtalFluor-E (1.5 equiv/2.5 equiv) with DAST/XtalFluor-E (1.5 equiv/ 1.0 equiv)	**3d** (51%) with full conversion

[a]Reactions were carried out under N_2 at −15 °C in 2 h, and 4 Å activated molecular sieves (powder) were used to remove deleterious moisture, unless stated otherwise.

[b]Amino-oxygenation product **4d** (42%) and benzoylated **2d** (24%) were isolated.

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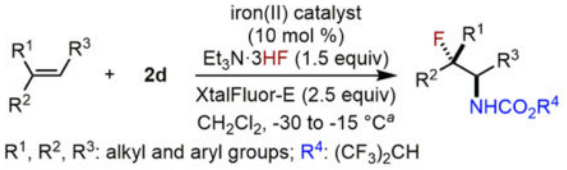
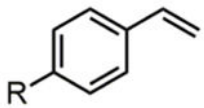
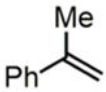
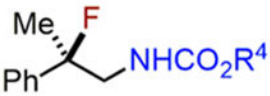
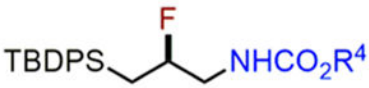
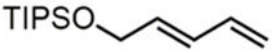
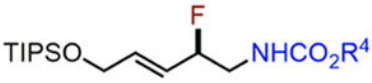
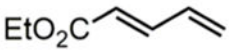
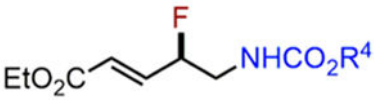
Table 3

Substrate Scope for the Iron-Catalyzed Olefin Aminofluorination



entry[a]	olefins	reaction time	vincinal fluoro carbamates	yield
1				
		2h	a:R=H	88%
		4h	b: R=Me[b]	82%
		3h	c: R=Br	87%
		4h	d: R=CO_2Me[b,c]	81%
2		4h		75%
3[b]		3h		83%
4		5h		82%
5[c,d]		3h		65%
6[e,f]		4h		65%

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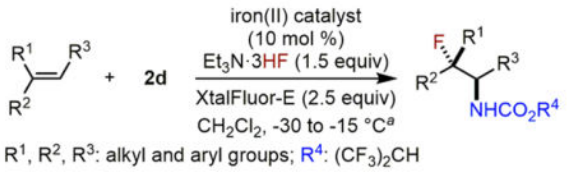
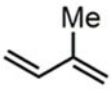
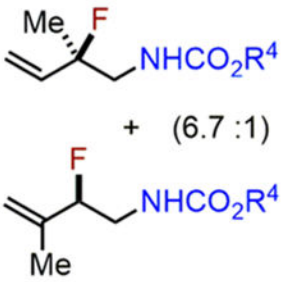
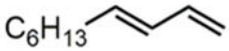
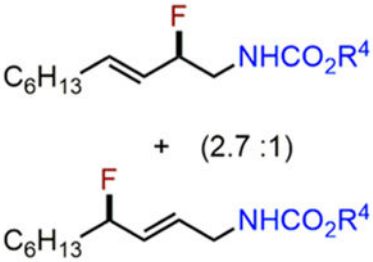
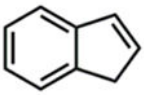
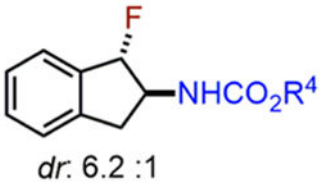
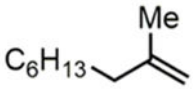
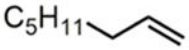


entry[a]	olefins	reaction time	vincinal fluoro carbamates	yield
7[d]		6h		84%
8[b]		6h		91%
9[c,g]		6h		72%
10[b,c]		3h		71%
11[f,h]		2h		62%

[a]Reactions were carried out under N_2 with preformed iron(II)–**L1** catalysts (10 mol %), unless stated otherwise.

[b]XtalFluor-E (3.0 equiv)/$Et_3N{\cdot}3HF$ (1.8 equiv).[21]

[c]Catalyst loading: 15 mol %.

[d]XtalFluor-E (4.0 equiv)/$Et_3N{\cdot}3HF$ (2.4 equiv).[21]

[e] Catalyst loading: 20 mol %.

[f] Additional XtalFluor-E (2.5 equiv)/$Et_3N{\cdot}3HF$ (2.5 equiv) were added after 1 h.[22]

[g] XtalFluor-E (5.0 equiv)/$Et_3N{\cdot}3HF$ (3.0 equiv).[21]

[h] Catalyst loading: 30 mol %, XtalFluor-E (1.5 equiv)/$Et_3N{\cdot}3HF$ (0.9 equiv).

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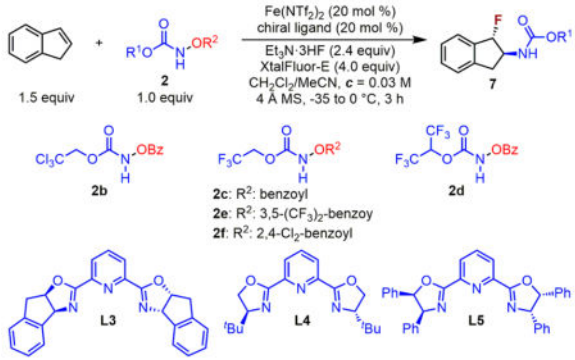
Table 4

Catalytic Asymmetric Indene Aminofluorination



entry[a]	2	ligand	yield[b]	dr[c]	ee (major/minor)[d]
1	**2d**	**L3**	48%	5.2:1	60%/60%
2	**2b**	**L3**	38%	2.5:1	78%/77%
3	**2c**	**L3**	35%	2.4:1	83%/82%
4	**2e**	**L3**	55%	2.2:1	55%/55%
5	**2f**	**L3**	59%	3.0:1	84%/84%
6	**2f**	**L4**	32%	1.8:1	36%/37%
7	**2f**	**L5**	39%	1.9:1	32%/30%

[a]Unless stated otherwise, the reactions were carried out under a nitrogen atmosphere with 4 Å molecular sieves.

[b]Isolated yield.

[c]dr was determined by ^{1}H NMR.

[d]Enantiomeric excess (ee) was measured by HPLC with chiral columns; the absolute stereochemistry was determined by X-ray crystallographic analysis of **7d** (R: $(CF_3)_2CH$).