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Iron(II)-Catalyzed Intramolecular Olefin Aminofluorination

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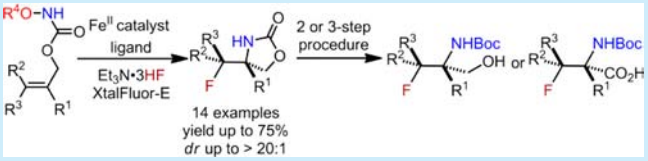
Supporting Information

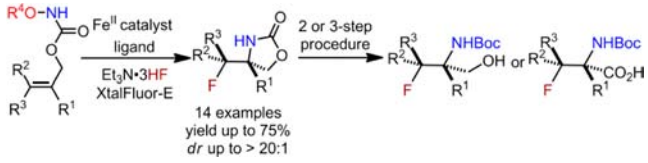
ABSTRACT: An iron(II)-catalyzed diastereoselective olefin aminofluorination is reported (dr up to >20:1). This new transformation applies a functionalized hydroxylamine and $Et_3N{\cdot}3HF$ as the nitrogen and fluorine source, which facilitates the efficient synthesis of β-fluoro primary amines and amino acids from allylic alcohol derivatives. Preliminary mechanistic studies reveal that an iron−nitrenoid is a possible intermediate and that its reactivity and enantioselectivity can be efficiently modulated by ligands.



Fluorinated organic molecules are valuable in medicinal chemistry because they are often associated with unique lipophilic and metabolic properties that are desirable in drug discovery.[1] More than 20% of the currently available pharmaceuticals contain at least one fluorine atom.[2] Therefore, an extensive amount of research has been devoted to the selective incorporation of fluorine atoms into medicinally relevant molecules. In addition to alcohol deoxyfluorination protocols,[3] a tremendous amount of progress has been made in the development of methods for sp^2 and sp^3 C−F bond formation.[4−6] Among those developments, methods for selective fluorine atom transfer via direct olefin aminofluorination have recently emerged. Liu reported palladium-catalyzed intramolecular olefin aminofluorination methods with hypervalent iodine and silver fluoride which afford fluorinated piperidines and (fluoromethyl)pyrrolidines.[7a,b] An intermolecular styrene aminofluorination method was reported by the same author.[7c] Li disclosed a silver-catalyzed intramolecular olefin aminofluorination method with Selectfluor, which yields fluorinated *N*-phenylpyrrolidinones.[7d] Recently, Toste developed an organocatalytic method for intramolecular 1,4-aminofluorination of conjugated dienes with Selectfluor.[7e] Despite these important discoveries, a method for direct olefin aminofluorination which yields β-fluoro primary amines, especially those with a tertiary fluoride moiety, has not been developed.[8] In addition, methods of iron-catalyzed or mediated selective fluorine atom transfer for olefin difunctionalization have been underexplored.[9]

We have recently reported an iron(II)-catalyzed intramolecular olefin aminohydroxylation that affords 1,2 *anti*-amino alcohols from *trans*-olefins.[10] Herein, we describe an iron(II)-catalyzed diastereoselective intramolecular olefin aminofluorination with a functionalized hydroxylamine and $Et_3N{\cdot}3HF$ (dr up to >20:1, Scheme 1). This reaction readily affords fluoro oxazolidinones which can then be conveniently converted to β-fluoro amines and amino acids. We also demonstrated that chiral ligands are effective in asymmetric induction (ee up to 81%). This method presents an expedient alternative to currently available β-fluoro amino acid synthesis methods that mostly rely on nucleophilic fluorination of alcohols and aziridines, and electrophilic fluorination of α-carbonyl compounds.[11]

Scheme 1. Iron-Catalyzed Intramolecular Olefin Aminofluorination



A cinnamyl alcohol-derived acyloxyl carbamate **1**[12] was selected as the model substrate for catalyst discovery (Table 1). Extensive experimentation revealed that both the benzoyl activating group and the iron catalysts with noncoordinating anions are crucial for the desired reactivity.[13] Among the iron catalysts examined, $Fe(BF_4)_2{\cdot}6H_2O$ exemplifies superior reactivity.[13] The $Fe(BF_4)_2$−1,10-phenanthroline (**L1**) complex alone catalyzes efficient aminohydroxylation of **1** and simultaneously leads to a small amount of fluoro oxazolidinone **2** (eq 1, entry 1, 9% yield, dr 1.8). However, in the presence of $Et_3N{\cdot}3HF$,[14] the same catalyst evidently promotes the aminofluoroination of olefin **1** (entry 2, 43% yield of **2**, dr 3.1). Concordantly, an aminohydroxylation product **3** was also detected (22% yield, dr >20:1). We subsequently applied Olah's reagent (HF−pyridine)[14] as the fluoride source and observed a similar result (entry 3, 37% yield, dr 3.0). We also noted that other slightly basic and more nucleophilic fluorine reagents lead to either rapid aziridination or substrate decomposition.[15]

These experimental results (entries 1−3) suggest that there are aminofluorination and aminohydroxylation pathways competing for a same reactive intermediate. We hypothesized that sequestering carboxylates may minimize the competing aminohydroxylation pathway. To our delight, the introduction of carboxylate trapping reagents such as XtalFluor-E indeed suppresses the competing aminohydroxylation and evidently

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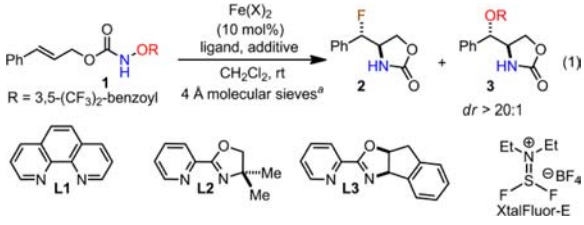
Table 1. Catalyst Discovery for the Iron-Catalyzed Olefin Aminofluorination



entry[b]	X[c]	ligand (mol %)	additive (equiv)	t (h)	yield (**2**)[d]	dr (**2**)[e]	yield (**3**)[d]
1	BF_4	**L1** (20)	none	5.0	9%	1.8	63%
2	BF_4	**L1** (20)	Et_3N·3HF (1.4)	5.0	43%	3.1	22%
3	BF_4	**L1** (20)	HF–Pyridine (1.4)	5.0	37%	3.0	25%
4	BF_4	**L1** (20)	Et_3N·3HF (1.4) XtalFluor-E (1.2)	4.0	61%	3.1	<5%
5	BF_4	**L1** (20)	XtalFluor-E (1.2)	5.0	<5%	NA	<5%
6	BF_4	**L2** (20)	Et_3N·3HF (1.4) XtalFluor-E (1.2)	4.0	58%	3.7	<5%
7	BF_4	**L3** (20)	Et_3N·3HF (1.4) XtalFluor-E (1.2)	1.5	72%	3.9	<5%
8	**BF_4**	**L3 (10)**	**Et_3N·3HF (1.4) XtalFluor-E (1.2)**	**1.0**	**71%**	**4.2**	**<5%**
9	NTf_2	**L3** (20)	Et_3N·3HF (1.6) XtalFluor-E (1.2)	3.5	75%	3.4	<5%

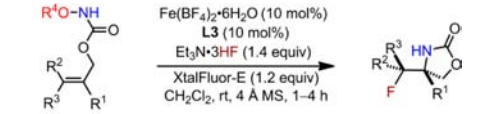
[a]Molecular sieves are necessary for catalyst activation; see the Supporting Information. [b]Reactions were carried out under argon at 23 °C. [c]$Fe(BF_4)_2$·$6H_2O$ or $Fe(NTf_2)_2$ was applied as the catalyst. [d]Isolated yield. [e]dr was determined by ^{19}F NMR analysis. NTf_2 = trifluoromethanesulfonimide.

increases the efficiency of aminofluorination (entry 4, 61% yield, dr 3.1).[16] We subsequently explored a range of carboxylate trapping reagents and determined that XtalFluor-E is superior than others.[17] Interestingly, in the absence of Et_3N·3HF, the $Fe(BF_4)_2$–**L1** complex and XtalFluor-E lead to decomposition of **1** (entry 5).

We thereby systematically examined a series of nitrogen-based ligands. We first observed that the hybrid pyridine–oxazoline ligand **L2** induces aminofluorination with a decreased yield (entry 6, 58% yield in 4 h, dr 3.7).[18] Interestingly, the hybrid ligand **L3** derived from (±) 1-amino indanol significantly accelerates the aminofluorination and increases selectivity (entry 7, 72% yield in 1.5 h, dr 3.9). Importantly, we discovered that a decreased ligand/metal ratio correlates with enhanced reactivity and dr (entry 8, 71% yield in 1 h, dr 4.2). Furthermore, we observed a detectable ee (23%) when the optically pure **L3** was applied as the chiral ligand. We also uncovered that $Fe(NTf_2)_2$ catalyzes a slower reaction with decreased dr yet with further increased yield (entry 9, 75% yield in 3.5 h, dr 3.4).

To explore the substrate scope of this transformation, we examined a variety of olefins under optimized conditions. We observed that *trans*-disubstituted styrenyl olefins are decent substrates (Table 2, entries 1–6). Aminofluorination of styrenyl olefins which have electron-donating groups affords *anti*-fluoro oxazolidinones with further increased dr (entries 2–3, dr up to 9.5). We also determined that a naphthyl olefin is a suitable substrate (entry 4, dr 10:1). However, substrates with electron-withdrawing groups suffer from modest dr in the delivery of *syn*-fluoro oxazolidinones (entries 5–6, dr 2.2–3.1).[19] This unique electronic effect is opposite to the effect we observed during the iron-catalyzed aminohydroxylation.[10] In addition to styrenyl olefins, both enynes and aliphatic-substituted olefins were found to be decent substrates (entries 7–8, dr 1.5–2.5). Following the latter with a two-step procedure (entry 8) provides 3-deoxy-3-fluoro safingol and sphinganine which are both fluorinated analogues of biologically active molecules.[20]

Table 2. Substrate Scope for the Iron-Catalyzed Olefin Aminofluorination



entry[a]	olefin	product	yield[b]	dr[b]
1	R^3 = Ph	*anti*	71%	4.2:1
2[c]	R^3 = 2-MePh	*anti*	62%	7.5:1
3[d]	R^3 = 4-MePh	*anti*	54%	9.5:1
4[d]	R^3 = α-Naphth	*anti*	59%	10:1
5[c]	R^3 = 4-CO_2MePh	*syn*	57%	3.1:1
6	R^3 = 3-ClPh	*anti*	61%	2.2:1
7	R^3 = Ph-C≡C	*anti*	73%	1.5:1
8	R^3 = *n*-$C_{15}H_{31}$	*anti*	64%	2.5:1
9	R^2 = Ph	*anti*	68%	4.2:1
10	R^2 = Ph-C≡C	*anti*	75%	1.5:1
11	R^2 = Me, R^3 = Ph	*syn*	45%	>20:1
12	R^2 = Me, R^3 = Me	*syn*	74%	NA
13			58%	>20:1
14			61%	2.4:1

[a]Reactions were carried out under argon at 23 °C. [b]Isolated yield; dr was determined by ^{19}F NMR analysis. [c]$Fe(NTf_2)_2$ (10 mol %), **L3** (20 mol %), Et_3N·3HF (1.6 equiv), XtalFluor-E (1.4 equiv). [d]R^4: benzoyl; $Fe(BF_4)_2$·$6H_2O$ (10 mol %), **L3** (10 mol %); Et_3N·3HF (1.8 equiv), XtalFluor-E (2.0 equiv).

Likewise, we demonstrated that *cis*-disubstituted olefins readily participate in this reaction and that essentially the same dr is observed for both the *cis* and *trans* isomers (entries 1,7 vs 9–10). The observed stereoconvergence suggests that the reaction occurs in a stepwise fashion. Moreover, we observed that the aminofluorination proceeds with trisubstituted olefins with excellent dr to afford a *syn*-fluoro oxazolidinone (entries 11–12, dr > 20:1).[21] Additionally, we determined that a cyclic substrate derived from a secondary allylic alcohol undergoes highly diastereoselective aminofluorination to afford an *anti*-fluoro oxazolidinone (entry 13, dr > 20:1).[21] We also noted that the corresponding acyclic substrate can be converted into an *anti*-fluoro oxazolidinone with modest dr (entry 14).[21]

To demonstrate the unique synthetic utility of the olefin aminofluorination method, we have converted *anti*-fluoro oxazolidinone **2a** to a protected *anti*-β-fluoro phenylalanine **4a**

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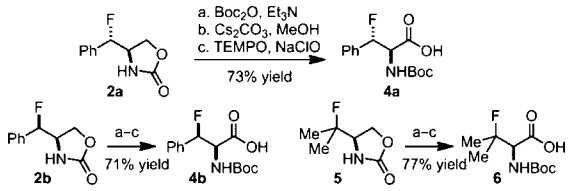
with excellent yield via a standard three-step procedure (Scheme 2). The same procedure has been applied to synthesize *syn*-β-fluoro phenylalanine **4b** and β-fluoro valine **6** in good overall yield (71−77%).

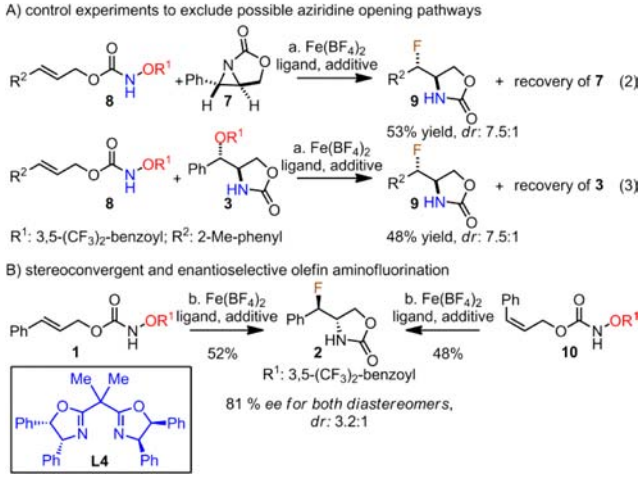
Scheme 2. Synthetic Applications: β-Fluoro Amino Acid Synthesis



[a]Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h. [b]Cs_2CO_3, MeOH, rt, 2 h. [c]TEMPO, TBAB, NaClO, $NaHCO_3$, 0 °C, 2 h. Boc = *tert*-butyloxycarbonyl; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; TBAB = tetra-*n*-butylammonium bromide.

In order to gain further mechanistic insight of this iron-catalyzed fluorine atom transfer process, we have performed several experiments (Scheme 3). First, we subjected both

Scheme 3. Control Experiments To Probe the Possible Mechanism



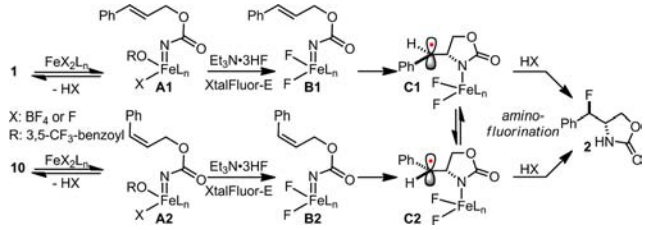
[a]$Fe(BF_4)_2{\cdot}6H_2O$ (10 mol %), **L3** (10 mol %); $Et_3N{\cdot}3HF$ (1.4 equiv), XtalFluor-E (1.2 equiv), CH_2Cl_2, rt, 4 Å molecular sieves, 24 h. [b]$Fe(BF_4)_2{\cdot}6H_2O$ (20 mol %), **L4** (20 mol %); $Et_3N{\cdot}3HF$ (1.4 equiv), XtalFluor-E (1.2 equiv), CH_2Cl_2, −30 °C, 4 Å molecular sieves, 12 h.

preformed aziridine **7** and β-benzyloxyl oxazolidinone **3** to catalytically active conditions and did not detect the amino-fluorination product **2** even after 24 h (eqs 2 and 3). These observations suggest that the aminofluorination unlikely proceeds through an aziridine or a β-benzyloxy oxazolidinone intermediate.

Furthermore, we observed that the iron-catalyzed asymmetric olefin aminofluorination is stereoconvergent: the isomeric olefins **1** and **10** are converted to fluoro oxazolidinone **2** with essentially the same ee (81%) and dr. These results and the ligand-enabled diastereoselectivity suggest that the iron−ligand complex is involved in the C−F and C−N bond formation processes.

Based on these experiments, a working hypothesis that best corroborates the mechanism of the iron-catalyzed intramolecular olefin aminofluorination is shown in Scheme 4. First, the iron complex can reductively cleave the N−O σ bond in the isomeric

Scheme 4. Mechanistic Working Hypothesis for the Iron-Catalyzed Olefin Aminofluorination



olefinic substrates **1** and **10**, possibly converting them to two iron-nitrenoids **A1** and **A2**, respectively.[22] Presumably, a competing aminohydroxylation can occur with **A1** and **A2** in the absence of external fluoride source to deliver the benzyloxyl oxazolidinone **3**.[10] However, in the presence of $Et_3N{\cdot}3HF$ and XtalFluor-E, a facile anion metathesis process may occur, which can convert **A1** and **A2** to iron fluoride-based nitrenoids **B1** and **B2**. From there, a stepwise cycloamination might occur, presumably converting **B1** and **B2** to two carbo-radical species **C1** and **C2** that are in a fast equilibrium. Subsequently, an oxidative fluoride ligand transfer can occur with either radical species **C1** or **C2**, affording the fluoro oxazolidinone **2**.[23] Alternatively, an electron transfer from the **C1**/**C2** radical species to the iron center followed by fluoride trapping of the generated carbocation may also lead to the final product **2**.

In summary, we have reported a new iron(II)-catalyzed diastereoselective olefin aminofluorination reaction with functionalized hydroxylamines and $Et_3N{\cdot}3HF$. This reaction readily transforms allylic alcohol derivatives to β-fluoro primary amines and amino acids after simple derivatization. Preliminary mechanistic studies revealed that an iron nitrenoid is a possible reactive intermediate for this stereoconvergent process. Our current effort focuses on the mechanistic understanding of this process and its applications in fluorinated nitrogen-containing molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data for all new compounds, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Alkoxy carbamates are unreactive, and *O*-sulfonyl hydroxyl carbmates are converted to aziridines under reaction conditions. $Fe(OTf)_2$, $Fe(NTf_2)_2$, and $Fe(ClO_4)_2$ are able to catalyze the reaction with significantly slower rates. FeF_2 is inactive to induce reactions. For reactivity of other acyloxyl carbamates, see the Supporting Information for details.

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(15) More nucleophilic fluoride sources, such as $Et_3N{\cdot}HF$, TBAF, lead to rapid aziridine formation. See the Supporting Information.

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