JOC The Journal of Organic Chemistry

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Regioselective Electrophilic Fluorination of Rationally Designed Imidazole Derivatives

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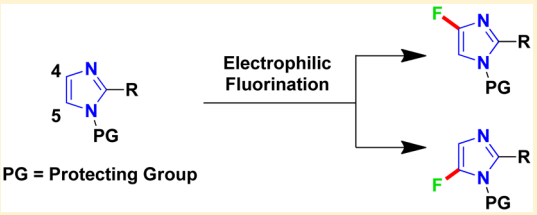
Supporting Information

ABSTRACT: We report the regioselective and direct functionalization of rationally designed imidazole derivatives through electrophilic fluorination with *N*-fluorobenzenesulfonimide enabled via in situ deprotonation with lithium 2,2,6,6-tetramethylpiperidine. Aided by a controlled protecting group switch, we were able to effectively target both the reactive 5- as well as the difficult to target 4-position of these molecules, leading to a series of fluorinated polysubstituted imidazoles in gram scale.

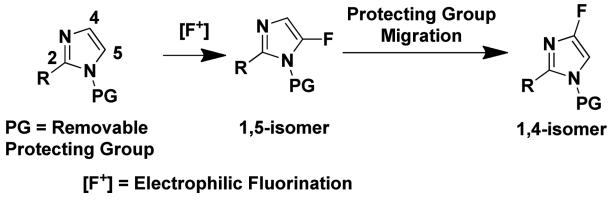


The incorporation of fluorine or fluorine-containing functional groups at specific positions within pharmaceutically relevant target molecules plays an increasingly important role in modern drug development.[1] This is due to the dramatic biological as well as chemical effects fluorine introduction offers such as increased metabolic stability, improved cellular permeability, and alteration of pK_a values of functionalities in close proximity.[2] Fluorinated molecules also play a major role in molecular imaging technologies such as positron emission tomography (PET).[3] Copious fluoroimidazole-containing target molecules display biologically interesting activities over a wide range of disease areas such as oncology, infectious diseases, or dermatology.[4]

However, few processes are applicable for the fluorination of heterocyclic systems such as imidazoles.[7] The first synthesis of fluorinated imidazole analogs was described in a seminal paper by the group of Kirk in the year 1971 via a Balz−Schiemann process[5] to obtain ethyl 4-fluoroimidazole-5-carboxylates in 38% yield.[8a] Since that time several other strategies have evolved to get access to these molecules including the construction from already fluorinated building blocks such as bistrifluoromethyl-substituted 1,3-azoles via a [4 + 1] cycloaddition reaction.[7a−c]

Fluoroimidazoles can also be obtained by Halex-type processes[6] through the displacement of leaving groups including halides[7d−g] or trimethyltin[7h] with nucleophilic fluorination reagents such as spray dried potassium fluoride to obtain 2-fluoro-1-methyl-1*H*-imidazole-4,5-dicarbonitrile in 82% yield.[7g] Another synthetic strategy to prepare fluorine-substituted imidazoles involves the use of electrophilic fluorinating reagents. The group of Hay took advantage of the fact that a 2-lithio imidazole readily reacts with gaseous perchloryl fluoride at −78 °C to form *N*-methyl-2-fluoroimidazole in 55% yield.[7i] Recently Jiang et al. reported the direct fluorination of *N*-methyl-imidazole-2-carboxylates with selectfluor in acetonitrile.[7j] Despite these excellent efforts, the direct fluorination of imidazoles is extremely underdeveloped,[7k,l] and most reported procedures rely on extremely toxic and difficult-to-handle reagents[7h,i,8] and show very limited substrate scope.[7i] In order to address this unmet synthetic need, we envisioned a reaction allowing for the efficient and regioselective incorporation of fluorine at selected positions within the imidazole moiety, utilizing nontoxic reaction partners. Encouraged by earlier work on electrophilic fluorination[7] as well as our own efforts on functionalization of imidazole analogs, demonstrating that 2-chloroimidazoles can be readily alkylated at position C5 via directed metalation,[9] we hypothesized that 5-fluoroimidazoles can be obtained under similar conditions and potentially isomerized via controlled protecting group migration to their 4-fluoro equivalents (Scheme 1). Weinreb and Lovely showed

Scheme 1. Regioselective Fluorination of Rationally Designed Imidazole Derivatives



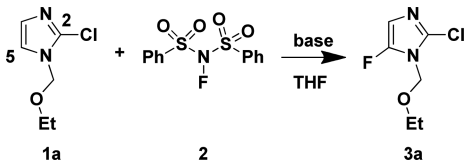
that 5-alkyl- as well as 5-iodo-substituted imidazole analogs equipped with N1-protecting groups such as benzyloxymethyl (BOM) or 2-(trimethylsilyl)ethoxymethyl (SEM) readily undergo isomerization via protecting group migration under thermodynamic conditions, aided by the addition of catalytic amounts of BOM-Cl and SEM-Cl, respectively.[10]

In an initial attempt to investigate the direct fluorination of substituted imidazole derivatives, we selected 2-chloro-1-(ethoxymethyl)-1*H*-imidazole **1a** as model substrate with *N*-fluorobenzenesulfonimide (NFSI) **2** as electrophilic fluorinating reagent[2b,11] and tetrahydrofuran (THF) as polar aprotic solvent (Table 1). The introduction of chlorine at position C2

Received: November 10, 2015
Published: January 7, 2016

DOI: 10.1021/acs.joc.5b02592
J. Org. Chem. 2016, 81, 1269−1276

Table 1. Effect of Different Bases on the Fluorination of 4a[a]



entry	base	temp (°C)	time (h)	yield[b]
1	–	20	24	–
2[c]	–	20	24	–
3[d]	$TMP_2Zn2MgCl_2$·LiCl	20	24	–
4[e]	TMPMgCl·LiCl	−78 to 20	24	–
5	*n*-BuLi	−78	1	53
6	LDA	−78	1	51
7	LTMP	−78	1	55

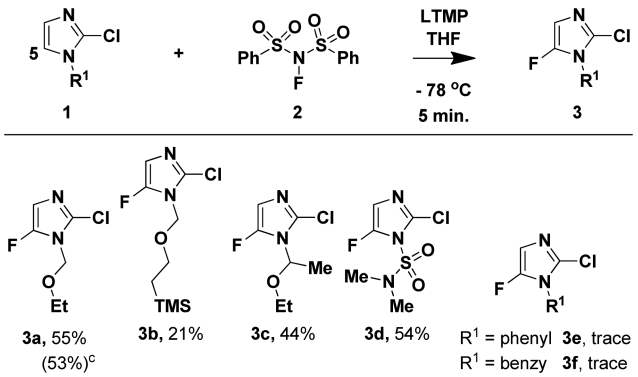
[a]Reaction conditions unless noted otherwise: **1a** (2.49 mmol, 1 equiv), **2** (2.74 mmol, 1.6 equiv), base (4.98 mmol, 2 equiv), THF (22 mL). [b]Percent conversion determined by ^{1}H NMR of the crude reaction mixture. [c]**1a** (0.31 mmol, 1 equiv), selectfluor used for fluorination (0.93 mmol, 3 equiv), acetonitrile (1.8 mL). [d]**1a** (1.25 mmol, 1 equiv), **2** (3.74 mmol, 3 equiv), THF (8 mL), base (0.88 mmol, 0.7 equiv). [e]**1a** (1.25 mmol, 1 equiv), **2** (2.5 mmol, 2 equiv), base (1.88 mmol, 1.5 equiv), THF (8 mL).

provides an electron-deficient functionality acting also as a cleavable protecting group,[12] potentially facilitating the direct fluorination at C5.

Imidazoles equipped with alkyloxymethyl ethers have previously been described as excellent reaction partners in transformations involving lithiation, potentially acting as ortho-directing groups.[13] Initial attempts to directly introduce fluorine at C5 in the absence of a strong base were unsuccessful (entries 1−2).

Inspired by the work of Knochel and others on directed metalation of aromatic as well as heteroaromatic ring systems and subsequent trapping with electrophiles,[14] we envisioned to selectively metalate imidazole **1a** at position C5 to facilitate the fluorination reaction at this position (entries 3−8). Direct zincation of **1a** with base complex $(TMP)_2Zn·2MgCl_2·2LiCl$ did not provide the desired product **3a** after 24 h at room temperature (entry 3). This is likely due to incomplete zinc incorporation as evidenced by iodination experiments. We then focused our attention on (TMP)MgCl·LiCl, which was added to a solution of starting material **1a** in THF at 0 °C. After 1 h at room temperature, the reaction mixture was cooled to −78 °C and subsequently reacted with **2** as a solution in THF. The reaction was allowed to slowly warm back up to room temperature. However, the transformation did not provide **3a** as product. The incorporation of other halides such as chlorine or bromine at position C5 through the same reaction conditions in the presence of TMPMgCl·LiCl resulted in haloimidazoles in yields of up to 76%. After failed attempts to fluorinate imidazole species **1a** at ambient temperatures, we treated the starting material with *n*-butyllithium (*n*-BuLi) at −78 °C followed by transfer of a precooled solution of NFSI **2** in THF (−78 °C) via a cannula. To our delight, the desired product **3a** was obtained in moderate yields (53%; entry 5). To further optimize the transformation, we exposed **1a** to the less nucleophilic base lithium diisopropylamide (LDA) under similar reaction conditions (entry 6). Unfortunately the reaction did not result in improved fluorine incorporation. In a subsequent attempt we treated **1a** with in situ generated lithium 2,2,6,6-tetramethylpiperidine (LTMP) at −78 °C and quenched the lithiated imidazole with NFSI **2** at the same temperature (transfer via cannula). Under these conditions the desired product **3a** was obtained in 55% yield (entry 7). After LTMP was identified as an optimal metalating reagent in this system, we focused our attention on the optimization of reaction conditions and investigated previously disclosed electrophilic fluorinating reagents including 2-fluoro-3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide, *N*-fluoro-pyridinium salts as well as selectfluor (see Supporting Information).[2b,11] Unfortunately none of the probed reagents provided the desired 5-fluoroimidazole **3a** in satisfactory yields. On the other hand, lowering the amount of LTMP to 1 equiv and decreasing the time of the transformation to 5 min resulted in no loss of reaction yield. With optimized reaction conditions at hand, we investigated various protecting groups in order to identify a removable N1-protecting group, that also can act as ortho-directing group during the metalation process (Scheme 2). Initially we investigated various linear and branched ether

Scheme 2. Evaluation of Various Imidazole Protecting Groups[a,b]



[a]Reaction conditions unless noted otherwise: **1a** (2.49 mmol, 1 equiv), **2** (2.74 mmol, 1.6 equiv), LTMP (2.49 mmol, 1 equiv), THF (22 mL). [b]Reaction yield based on isolation of **3**. [c]**1a** (9.25 mmol, 1 equiv), **5** (14.80 mmol, 1.6 equiv), LTMP (9.25 mmol, 1 equiv), THF (81 mL).

derivatives, similar to those disclosed in the context of base-mediated electrophilic derivatization of imidazoles or pyrazoles (compounds **3b** and **3c**).[10,15] Imidazole derivative **1b** equipped with a 2-(trimethylsilyl)ethoxymethyl ether (SEM) provided the desired fluoroimidazole **3b** in 21% yield. If branched ethoxyethyl derived imidazole **1c** was used, 44% of the desired product **3c** was obtained.

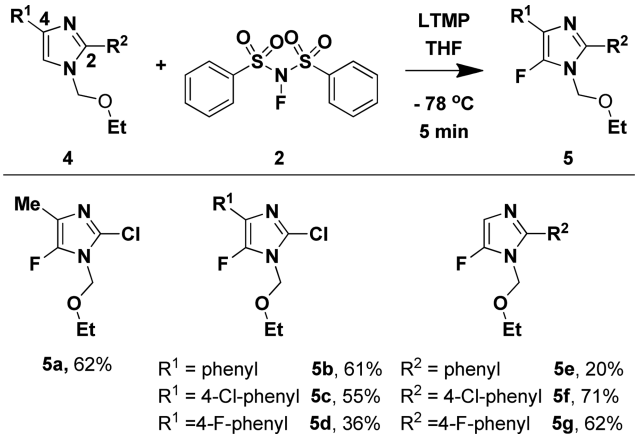
N,*N*-dimethylsulfamoyl protection is frequently utilized in the context of alkylation reactions of imidazole structures.[16] When applied under our reaction conditions, the desired 5-fluoroimidazole **3d** was obtained in 54% yield.

Both benzyl as well as phenyl-substituted substrates did not allow for the efficient introduction of fluorine (**3e** and **3f**). This might be explained due to the poor ortho-directing capabilities of these two functionalities. After we demonstrated that ethoxymethyl ether-substituted imidazole **1a** allowed for the highest incorporation of fluorine at position C5 in milligram and gram scale, we evaluated the generality of the developed methodology (Scheme 3).

Initially we focused on various substituents at position C4 on the imidazole ring system. Sterically more demanding functionalities such as methyl or phenyl are well tolerated under the probed reaction conditions, whereas electron-

DOI: 10.1021/acs.joc.5b02592
J. Org. Chem. 2016, 81, 1269−1276

Scheme 3. Scope of the Reaction[a,b]

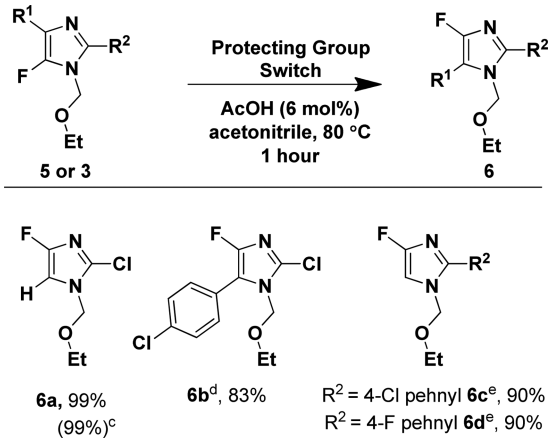


[a]Reaction conditions unless noted otherwise: **4a** (2.49 mmol, 1 equiv), **2** (2.74 mmol, 1.6 equiv), LTMP (2.49 mmol, 1 equiv), THF (22 mL). [b]Reaction yield based on isolation of **5**.

withdrawing halogens in the para position of the aryl substituent resulted in a significant loss of reaction yield (**5d**). 4-methyl-functionalized imidazole **4a** provided the desired product **5a** in 62% yield. If phenyl-substituted electron neutral imidazole **4b** was applied in the reaction, product **5b** was isolated in an increased yield of 61% compared to the parent compound **3a** (Scheme 2). Incorporation of electronegative halogen substituents in the para position of the phenyl ring resulted in successive loss of reaction yield (**5c**: 55%; **5d**: 36%). Electronic effects might in part contribute to proto demetalation, evidenced by the recovery of unreacted starting materials, even though great care was taken to exclude moisture from the system. To further evaluate the scope of the reaction, we investigated various functional groups to replace chlorine at position C2 (**5e**−**g**). We were delighted to find that 2-aryl derived imidazoles provided the desired fluorinated products in yields of up to 71%. Even though simple electron neutral 2-phenyl-imidazole **4e** afforded **5e** only in 20% yield, 4-chlorophenyl as well as 4-fluorophenyl analogs were successfully converted to fluorinated products **5f** (71%) and **5g** (61%). Overall, the obtained reaction yields (**5a**−**g**) are rather substrate specific and do not necessarily follow electronic factors. Even though products functionalized at C4 (**5a**−**e**) seem to suggest that electronegative substituents are disfavored, compounds **5e**−**g** equipped with aryl-substituents at position C2 demonstrate that a fluorine in the para position is tolerated, whereas more electron neutral phenyl provided only low yields. Finally we investigated if the obtained 5-fluoroimidazoles can be converted to otherwise difficult to obtain 4-fluoro analogs, via a simple controlled protecting group migration (Scheme 4). And indeed, we were delighted to find that imidazole derivatives equipped with various C2 substituents ranging from chlorine to aryl as well as aromatic C4 substituents undergo the protecting group migration. If compound **3a** was dissolved in acetonitrile in the presence of a catalytic amount of acetic acid (AcOH) followed by heating to 80 °C for 1 h, the desired product **6a** was obtained in almost quantitative yield.

3a also converts to the corresponding 4-fluoroimidazole under neat conditions at 40 °C after 2.5 h. 4-chlorophenyl-5-fluoroimidazole **5c** was converted to **6b** in 83% yield, however, an increased reaction time of 4h was necessary to complete the reaction, suggesting that steric factors have an influence on the

Scheme 4. Controlled Protecting Group Migration[a,b]



[a]Reaction conditions unless noted otherwise: **5** (0.20 mmol, 1 equiv), AcOH (0.013 mmol, 0.06 equiv), acetonitrile (0.25 mL). [b]Reaction yield based on isolation of **6**. [c]**5a** (2.8 mmol, 1 equiv), AcOH (0.013 mmol, 0.06 equiv), acetonitrile (0.25 mL). [d]Reaction time 4 h. [e]Reaction time 24 h.

yield of the reaction. Similarly, compounds **5f** and **5g** were converted to the desired 4-fluoroimidazole analogs **6c** and **6d** after 4h. The longer reaction time of products **6c** and **6d**, lacking the 2-chloro substituent compared to the more electron-deficient **6a**, suggests the possibility that electronic factors also contribute to the outcome of the reaction. In Scheme 5 a possible intermolecular mechanism for this transformation is depicted involving an acid-catalyzed S_N2-type reaction, similar to previously suggested mechanisms involving protecting group migrations in imidazole species.[10] Bisethoxymethyl-substituted imidazolium salt **8** is formed via nucleophilic attack of nitrogen N3 embedded in fluoroimidazole **3a**, on protonated imidazole 7. In a subsequent step, **8** collapses to form two 4-fluoro-substituted products **6a**. Other reaction mechanisms including S_N1-type processes, however, cannot be ruled out completely.

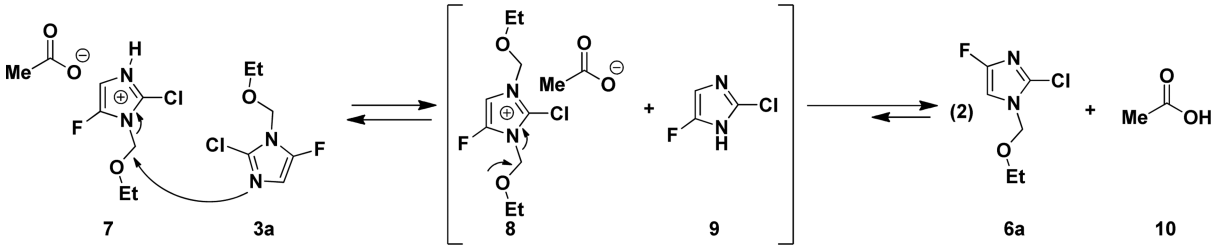
We have demonstrated that a diverse set of complex polysubstituted fluorinated imidazole derivatives can be efficiently obtained through a LTMP enabled process with NFSI as electrophilic fluorinating reagent. Aryl- and halide- as well as alkyl-substituted starting materials were good substrates in the disclosed transformation. Via a protecting group migration from nitrogen N1 to N3 both 5- as well as the otherwise difficult to obtain 4-substituted imidazoles are accessible through this strategy in an atom economic manner. The newly developed technology might also provide a valuable tool for the direct fluorination of other five- and six-membered heterocyclic systems such as pyrazoles as well as pyrimidines. Research efforts in this context are ongoing.

EXPERIMENTAL SECTION

General Methods. Reagents were purchased from commercial sources and used without further purification unless otherwise noted. ^{1}H NMR (400, 500, 600 MHz), ^{13}C NMR (101, 126, 150 MHz), and ^{19}F (400, 500, 600 MHz) spectra were acquired on 400 and 500 as well as 600 NMR spectrometers. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane as internal standard. Spin multiplets are reported as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra were recorded using a uTOF

DOI: 10.1021/acs.joc.5b02592
J. Org. Chem. 2016, 81, 1269−1276

Scheme 5. Plausible Mechanism for the Protecting Group Migration



spectrometer in electrospray mode, coupled with an HPLC, and internally calibrated with sodium formate.

General Procedure for the Fluorination of Imidazole Derivatives (A). To freshly distilled 2,2,6,6-tetramethylpiperidine (TMP) under nitrogen in a three-neck round-bottom flask equipped with a Schlenck line is added THF and cooled to −78 °C. *n*-BuLi (2.5M, hexanes) is slowly added to the solution at the same temperature, and the reaction is stirred for 30 min at −78 °C. The protected imidazole derivative is dissolved in THF and slowly added to the reaction mixture containing LTMP (temperature should be kept below −70 °C). After 10 min, NFSI, dissolved in THF and precooled to −78 °C, is transferred to the reaction mixture via a cannula (−78 °C). After 5 min at the same temperature, the reaction is quenched with water and saturated NH_4Cl at −78 °C and allowed to warm to room temperature. The reaction mixture was extracted with DCM, and the organic fractions were combined and dried over Na_2SO_4. After the solvents were removed by evaporation under reduced pressure, the crude reaction product was subjected to silica gel purification.

General Procedure for the Controlled Protecting Group Migration (B). 5-Fluoroimidazole **5** was dissolved in acetonitrile and 5 mol % of acetic acid. The reaction vessel was sealed and heated to 80 °C until complete isomerization to 4-fluoroimidazole **6**, as indicated by ^{1}H NMR of the crude reaction mixture. A solution of saturated sodium carbonate (Na_2CO_3) was added, and the reaction product was extracted with DCM.

*2-Chloro-1-(ethoxymethyl)-5-fluoro-1H-imidazole (**3a**).* Synthesized according to General Procedure A. 2-chloro-1-(ethoxymethyl)-1*H*-imidazole (**1a**) (400 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 8:2) and **3a** was obtained in 55% yield (245 mg, 1.37 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.46 (d, J = 7.4 Hz, 1H), 5.24 (d, J = 0.8 Hz, 2H), 3.57 (dd, J = 7.1, 0.8 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.8 (d, J = 276 Hz), 125.5 (d, J = 10.0 Hz), 105.4, 72.4, 65.2, 14.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −146.9 (d, J = 7.2 Hz). HRMS calcd for $C_6H_8ClFN_2O$ [M + H]$^+$ 179.0382, found 179.0393.

*2-Chloro-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**3b**).* Synthesized according to General Procedure A. 2-chloro-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (**1b**) (580 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 8:2), and **3b** was obtained in 21% yield (131 mg, 0.52 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, J = 7.5 Hz, 1H), 5.25−5.20 (m, 1H), 3.62−3.58 (m, 1H), 0.95−0.91 (m, 1H), 0.00 (s, 7H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2 (d, J = 276.0 Hz), 126.9−125.3 (m), 106.7 (d, J = 7.9 Hz), 73.4, 68.6, 19.2, −0.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −146.9 (d, J = 7.6 Hz). HRMS calcd for $C_9H_{16}ClFN_2OSi$ [M] 250.0705, found 250.0700 (**3b** was analyzed by GCMS with quadrupole mass analyzer; a post-acquisition software package was used to obtain high mass accuracy).

*2-Chloro-1-(1-ethoxyethyl)-5-fluoro-1H-imidazole (**3c**).* Synthesized according to General Procedure A. Compound **3c** isomerizes to 2-chloro-1-(1-ethoxyethyl)-4-fluoro-1*H*-imidazole during workup. 2-Chloro-1-(1-ethoxyethyl)-1*H*-imidazole (435 mg, 2.49 mmol) (**1c**) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 8:2), and **3c** was obtained in 44% yield (211 mg, 1.10 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J = 8.1 Hz, 1H), 5.51−5.46 (m, 1H), 3.42 (dd, J = 18.9, 7.0 Hz, 2H), 1.57 (d, J = 5.9 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6 (d, J = 239.74 Hz), 124.5 (d, J = 19.8 Hz), 95.6, 83.3, 64.5, 22.6, 14.8.^{19}F NMR (376 MHz, $CDCl_3$) δ −131.8 (d, J = 8.1 Hz). HRMS calcd for $C_7H_{10}ClFN_2O$ [M + H]$^+$ 193.0538, found 193.0540.

*2-Chloro-5-fluoro-N,N-dimethyl-1H-imidazole-1-sulfonamide (**3d**).* Synthesized according to General Procedure A. 2-Chloro-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**1d**) (522 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (DCM: ether, 93:7), and **3d** was obtained in 54% yield (306 mg, 1.34 mmol). ^{1}H NMR (600 MHz, MeOD) δ 6.64 (d, J = 7.9 Hz, 1H), 2.95 (s, 6H). ^{13}C NMR (151 MHz, MeOD) δ 156.6 (d, J = 236.9 Hz), 125.6 (d, J = 19.6 Hz), 97.7 (d, J = 36.2 Hz), 39.8.^{19}F NMR (376 MHz, MeOD) δ-138.1 (d, J = 10.5 Hz). HRMS calcd for $C_5H_7ClFN_3O_2S$ [M + H]$^+$ 228.0004, found 228.0005.

*1-Benzyl-2-chloro-5-fluoro-1H-imidazole (**3e**).* Synthesized according to General Procedure A. 1-benzyl-2-chloro-1*H*-imidazole (**1e**) (480 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup, and **3e** was obtained in trace amount.

*2-Chloro-5-fluoro-1-phenyl-1H-imidazole (**3f**).* Synthesized according to General Procedure A. 2-Chloro-1-phenyl-1*H*-imidazole (**1f**) (445 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 9:1), and **3f** was obtained in trace amount.

*2-Chloro-1-(ethoxymethyl)-5-fluoro-4-methyl-1H-imidazole (**5a**).* Synthesized according to General Procedure A. 2-Chloro-1-(ethoxymethyl)-4-methyl-1*H*-imidazole (**4a**) (435 mg, 2.49 mmol) dissolved

DOI: 10.1021/acs.joc.5b02592
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in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 9:1), and **5a** was obtained in 62% yield (296 mg, 1.54 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (d, *J* = 0.8 Hz, 2H), 3.59−3.53 (m, 2H), 2.11 (d, *J* = 1.8 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9 (d, *J* = 272.6 Hz), 123.6 (d, *J* = 11.5 Hz), 113.2 (d, *J* = 6.8 Hz), 72.33, 65.0, 14.7, 10.5 (d, *J* = 4.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.2. HRMS calcd for $C_7H_{10}ClFN_2O$ $[M + H]^+$ 193.0538, found 193.0539.

*2-Chloro-1-(ethoxymethyl)-5-fluoro-4-phenyl-1H-imidazole (**5b**).* Synthesized according to General Procedure A. 2-Chloro-1-(ethoxymethyl)-4-phenyl-1*H*-imidazole (**4b**) (590 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 9:1), and **5b** was obtained in 61% yield (350 mg, 1.37 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.71 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.27−7.24 (m, 1H), 5.29 (d, *J* = 0.9 Hz, 2H), 3.65−3.59 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.7 (d, *J* = 280.7 Hz), 131.0 (d, *J* = 5.4 Hz), 128.8, 127.2, 125.2 (d, *J* = 4.4 Hz), 117.7 (d, *J* = 1.7 Hz), 72.8, 65.4, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −144.2. HRMS calcd for $C_{12}H_{12}ClFN_2O$ $[M + H]^+$ 255.0695, found 255.0690.

*2-Chloro-4-(4-chlorophenyl)-1-(ethoxymethyl)-5-fluoro-1H-imidazole (**5c**).* Synthesized according to General Procedure A. 2-Chloro-4-(4-chlorophenyl)-1-(ethoxymethyl)-1*H*-imidazole (**4c**) (675 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 9:1), and **5c** was obtained in 55% yield (395 mg, 1.37 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 2H), 7.38−7.34 (m, 2H), 5.29 (d, *J* = 0.9 Hz, 2H), 3.65−3.59 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.7 (d, *J* = 281.0 Hz), 132.8, 129.6 (d, *J* = 5.6 Hz), 129.5, 126.4 (d, *J* = 4.4 Hz), 125.4 (d, *J* = 11.1 Hz), 116.8 (d, *J* = 2.0 Hz), 72.8, 65.4, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −143.6. HRMS calcd for $C_{12}H_{11}Cl_2FN_2O$ $[M + H]^+$ 289.0305, found 289.0314.

*2-Chloro-1-(ethoxymethyl)-5-fluoro-4-(4-fluorophenyl)-1H-imidazole (**5d**).* Synthesized according to General Procedure A. 2-Chloro-1-(ethoxymethyl)-4-(4-fluorophenyl)-1*H*-imidazole (**4d**) (634 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (hexanes: EtOAc, 9:1), and **5d** was obtained in 39% yield (244 mg, 0.90 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 5.28 (d, *J* = 0.9 Hz, 2H), 3.65−3.59 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.2 Hz), 143.3 (d, *J* = 279.9 Hz), 133.8, 129.3, 128.5 (d, *J* = 5.1 Hz), 128.0, 127.3(dd, *J* = 5.5, 3.2 Hz), 127.08 (dd, *J* = 8.0, 4.4 Hz), 125.4 (d, *J* = 11.3 Hz), 117.1(d, *J* = 2.0 Hz), 115.7 (d, *J* = 21.6 Hz), 72.8, 65.4, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.8, −145.0. HRMS calcd for $C_{12}H_{11}ClF_2N_2O$ $[M + H]^+$ 273.0601, found 273.0612.

*1-(Ethoxymethyl)-5-fluoro-2-phenyl-1H-imidazole (**5e**).* Synthesized according to General Procedure A. 1-(Ethoxymethyl)-2-phenyl-1*H*-imidazole (**4e**) (504 mg, 2.49) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (DCM:ether:hexanes, 93:7:100), and **5e** was obtained in 20% yield (110 mg, 0.45 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.48−7.40 (m, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 1.2 Hz, 2H), 3.64 (dd, *J* = 7.1, 1.3 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.1 (d, *J* = 273.5 Hz), 141.8 (d, *J* = 5.7 Hz), 130.2, 129.2, 128.9,, 105.3 (d, *J* = 8.0 Hz), 72.2, 64.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −150.9 (d, *J* = 8.0 Hz). HRMS calcd for $C12_2H_{13}FN_2O$ $[M + H]^+$ 221.1085, found 221.1089.

*2-(4-Chlorophenyl)-1-(ethoxymethyl)-5-fluoro-1H-imidazole (**5f**).* Synthesized according to General Procedure A. 2-(4-Chlorophenyl)-1-(ethoxymethyl)-1*H*-imidazole (**4f**) (590 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (DCM:ether:hexanes, 93:7:100), and **5f** was obtained in 71% yield (450 mg, 1.77 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 2H), 3.67 (qd, *J* = 7.0, 1.3 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.0 (d, *J* = 274.1 Hz), 140.6 (d, *J* = 5.8 Hz), 135.3, 129.6, 129.0, 128.4, 105.3 (d, *J* = 7.6 Hz), 72.0, 64.9, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −150.5 (d, *J* = 7.8 Hz). HRMS calcd for $C_{12}H_{12}ClFN_2O$ $[M + H]^+$ 255.0695, found 255.0692.

*1-(Ethoxymethyl)-5-fluoro-2-(4-fluorophenyl)-1H-imidazole (**5g**).* Synthesized according to General Procedure A. 1-(Ethoxymethyl)-2-(4-fluorophenyl)-1*H*-imidazole (**4g**) (549 mg, 2.49 mmol) dissolved in 4 mL THF was added slowly to a reaction mixture containing TMP (420 μL, 2.49 mmol) and *n*-BuLi (996 μL, 2.49 mmol) in 9 mL THF at −78 °C. After 30 min at the same temperature, NFSI (1.26g, 3.99 mmol) dissolved in 9 mL THF and precooled to −78 °C is transferred to the reaction mixture via a cannula. After 5 min, the reaction mixture was subjected to aqueous workup and silica gel purification (DCM:ether:hexanes, 93:7:100), and **5g** was obtained in 62% yield (362 mg, 1.52 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.19−7.11 (m, 2H), 6.641 (d, *J* = 7.6 Hz, 1H), 5.20 (s, 2H), 3.67 (qd, *J* = 7.0, 1.4 Hz, 2H), 1.27 (t, *J* = 8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3 (d, *J* = 249.4 Hz), 148.8 (d, *J* = 273.6 Hz), 140.8 (d, *J* = 5.7 Hz), 130.4 (d, *J* = 8.3 Hz), 126.1 (d, *J* = 3.2 Hz), 115.9 (d, *J* = 21.1 Hz), 105.0 (d, *J* = 8.0 Hz), 72.0, 64.8, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.7, −150.9 (d, *J* = 9.1 Hz). HRMS calcd for $C_{12}H_{12}F_2N_2O$ $[M + H]^+$ 239.0990, found 239.0989.

*2-Chloro-1-(ethoxymethyl)-4-fluoro-1H-imidazole (**6a**).* Synthesized according to General Procedure B. 2-Chloro-1-(ethoxymethyl)-5-fluoro-1*H*-imidazole (**3a**) (500 mg, 2.80 mmol) was reacted in the presence of acetonitrile (3.5 mL) and of acetic acid (8 μL, 0.14 mmol) at 80 °C for 1 h. After aqueous work up with saturated sodium carbonate (Na_2CO_3) and extraction with DCM, followed by silica gel purification, **6a** was obtained in quantitative yield (500 mg, 2.80 mmol). **3a** also isomerizes to **6a** if stored under neat conditions at 40 °C for 2.5 h. ^{1}H NMR (400 MHz, $CDCl_3$) 6.58 (d, *J* = 8.0 Hz, 1H), 5.24 (d, *J* = 1.2 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.2 (d, *J* = 239.7 Hz), 126.0 (d, *J* = 19.3 Hz), 99.5 (d, *J* = 36.2 Hz), 75.9, 65.0, 14.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −132.6 (d, *J* = 8.1 Hz). HRMS calcd for $C_6H_8ClFN_2O$ $[M + H]^+$ 179.0382, found 179.0382.

*2-Chloro-5-(4-chlorophenyl)-1-(ethoxymethyl)-4-fluoro-1H-imidazole (**6b**).* Synthesized according to General Procedure B. 2-Chloro-4-(4-chlorophenyl)-1-(ethoxymethyl)-5-fluoro-1*H*-imidazole **5c** (80 mg, 0.28 mmol) was reacted in the presence of acetonitrile (0.55 mL) and acetic acid (0.8 μL, 0.014 mmol) at 80 °C for 4 h. After aqueous work up with saturated sodium carbonate (Na_2CO_3) and extraction with DCM, followed by silica gel purification, **6b** was obtained in yield 83% yield (66 mg, 0.23 mmol). ^{1}H NMR (500 MHz,

DOI: 10.1021/acs.joc.5b02592
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$CDCl_3$) δ 7.53−7.47 (m, 2H), 7.46−7.40 (m, 2H), 5.23 (d, J = 1.2 Hz, 2H), 3.63 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.0 (d, J = 242.4 Hz), 134.6, 130.3 (d, J = 2.4 Hz), 129.4, 127.3 (d, J = 20.0 Hz), 125.2 (d, J = 4.7 Hz), 112.6 (d, J = 29.5 Hz), 73.8, 65.0, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.5. HRMS calcd for $C_{12}H_{11}Cl_2FN_2O$ $[M + H]^+$ 289.0305, found 289.0319.

*2-(4-Chlorophenyl)-1-(ethoxymethyl)-4-fluoro-1H-imidazole (**6c**).* Synthesized according to General Procedure B. 2-(4-Chlorophenyl)-1-(ethoxymethyl)-5-fluoro-1*H*-imidazole **5f** (50 mg, 0.21 mmol) was reacted in the presence of acetonitrile (0.42 mL) and acetic acid (0.7 μL, 0.013 mmol) at 80 °C for 24 h. After aqueous work up with saturated sodium carbonate (Na_2CO_3) and extraction with DCM, followed by silica gel purification, **6c** was obtained in yield 90% yield (45 mg, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.65 (m, 2H), 7.50−7.36 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 5.20 (d, J = 1.2 Hz, 2H), 3.59 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7 (d, J = 235.1 Hz), 141.2 (d, J = 15.1 Hz), 135.6, 130.2, 129.1, 127.9, 100.0 (d, J = 37.7 Hz), 76.3, 64.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.7 (d, J = 8.2 Hz). HRMS calcd for $C_{12}H_{12}ClFN_2O$ $[M + H]^+$ 255.0695, found 255.0698.

*1-(Ethoxymethyl)-4-fluoro-2-(4-fluorophenyl)-1H-imidazole (**6d**).* Synthesized according to General Procedure B. 1-(Ethoxymethyl)-5-fluoro-2-(4-fluorophenyl)-1*H*-imidazole **5g** (50 mg, 0.21 mmol) was reacted in the presence of acetonitrile (0.42 mL) and acetic acid (0.7 μL, 0.013 mmol) at 80 °C for 24 h. After aqueous work up with saturated sodium carbonate (Na_2CO_3) and extraction with DCM, followed by silica gel purification, **6d** was obtained in 90% yield (45 mg, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.68 (m, 2H), 7.22−7.07 (m, 2H), 6.68−6.59 (d, J = 8.2 Hz, 1H), 5.2 (d, J = 1.2 Hz, 2H), 3.59 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5 (d, J = 249.9 Hz), 156.6 (d, J = 235.0 Hz), 141.4 (d, J = 15.2 Hz), 131.0, 130.0, 125.6 (d, J = 3.3 Hz), 116.0, 115.9, 99.6 (d, J = 37.8 Hz), 76.3, 64.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.3, −136.0 (d, J = 9.3 Hz). HRMS calcd for $C_{12}H_{12}F_2N_2O$ $[M + H]^+$ 239.0990, found 239.0986.

*2-Chloro-1-(ethoxymethyl)-1H-imidazole (**1a**).*[17,19] 1*H*-imidazole (10 g, 146.89 mmol) in THF (140 mL) was reacted with NaH (60% dispersion in oil) (23.5 g, 0.588 mol) and chloromethyl ethyl ether (16.66g, 0.176 mol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and 1-(ethoxymethyl)-1*H*-imidazole was obtained in 84% yield (15.71g, 0.123 mol). 1-(Ethoxymethyl)-1*H*-imidazole (7.7 g, 60.80 mmol) was dissolved in 60 mL THF and treated with TMPMgCl·LiCl (91.2 mL, 91.20 mmol) and hexachloroethane dissolved in 55 mL THF (15.83g, 66.88 mmol) at −25 °C. After aqueous workup, the crude product was subjected to silica gel purification (8:2 hexanes:ethyl acetate), and (**1a**) was obtained in 71% yield (7.34g, 31.93 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 1.6 Hz, 1H), 5.28 (s, 2H), 3.51 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.3, 128.8, 121.0, 75.4, 64.6, 14.7. HRMS calcd for $C_6H_9ClN_2O$ $[M + H]^+$ 161.0476, found 161.0477.

*2-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**1b**).*[17] NaH (60% dispersion in mineral oil) (1.56 g; 39.02 mmol) and 2-chloro-1*H*-imidazole (1.0 g; 9.75 mmol) in THF at 0 °C were reacted for 30 min. 2-(Trimethylsilyl)ethoxymethyl chloride (1.95g; 11.71 mmol) was added at 0 °C, and the mixture was allowed to continue for 3 h at room temperature. After aqueous work up, the crude reaction mixture was subject to silica gel chromatography (hexanes: EtOAc; 8:2), and **1b** was obtained in 97% yield (2.21g, 9.49 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 1.5 Hz, 1H), 5.27 (s, 2H), 3.56−3.51 (m, 2H), 0.94−0.89 (m, 2H), 0.00 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.4, 128.9, 121.1, 75.2, 66.7, 17.8, −1.3. HRMS calcd for $C_9H_{17}ClN_2OSi$ $[M + H]^+$ 233.0871, found 233.0865.

*2-Chloro-1-(1-ethoxyethyl)-1H-imidazole (**1c**).*[17] NaH (60% dispersion in mineral oil) (1.56g; 39.02 mmol) and 2-chloro-1*H*-imidazole (1.0 g; 9.75 mmol) in THF at 0 °C were reacted for 30 min. 1-Chloro-1-ethoxyethane[18] (1.27g; 11.71 mmol) was added at 0 °C, and the mixture was allowed to continue for 3 h at room temperature. After aqueous work up, the crude reaction mixture was subject to silica gel chromatography (hexanes: EtOAc; 8:2), and **1c** was obtained in 89% yield (1.51g, 8.65 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 1.6 Hz, 1H), 7.00 (dd, J = 1.5, 0.6 Hz, 1H), 5.51 (q, J = 5.9 Hz, 1H), 3.50−3.27 (m,, 2H), 1.60 (d, J = 5.9 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 130., 129.0, 116., 82.7, 64.2, 22.6, 14.7. HRMS calcd for $C_7H_{11}ClN_2O$ [M] 174.0554, found 174.0529 (**1c** was analyzed by GCMS with quadrupole mass analyzer; a postacquisition software package was used to obtain high mass accuracy).

*2-Chloro-N,N-dimethyl-1H-imidazole-1-sulfonamide (**1d**).*[17] NaH (60% dispersion in mineral oil) (1.56g; 39.02 mmol) and 2-chloro-1*H*-imidazole (1.0 g; 9.75 mmol) in THF at 0 °C were reacted for 30 min. Dimethylsulfamoyl chloride (1.68g; 11.71 mmol) was added at 0 °C, and the mixture was allowed to continue for 3 h at room temperature. After aqueous work up, the crude reaction mixture was subject to silica gel chromatography (hexanes: EtOAc; 6:4), and **1d** was obtained in 55% yield (1.12g, 5.34 mmol). Analysis data are in accordance with previously disclosed substrate.

*1-Benzyl-2-chloro-1H-imidazole (**1e**).*[19] 1-Benzyl-1*H*-imidazole (7.91g; 50 mmol) was dissolved in 50 mL THF and reacted with TMPMgCl·LiCl (1 M THF/toluene) (75 mL; 75 mmol) and hexachloroethane (13.02g; 55 mmol) dissolved in 55 mL THF. After aqueous workup, the crude product was subjected to silica gel purification (hexanes: EtOAc 9:1), and product **1e** was obtained in 71.5% (6.89g, 35.77 mmol). Analysis data are in accordance with previously disclosed substrate.

*2-Chloro-phenyl-1H-imidazole (**1f**).* To 1-pheny-1*H*-limidazole (3g, 20.81 mmol) dissolved in THF (12 mL), *n*-BuLi (2.5 M in hexanes) (9.16gml, 22.89 mmol) was added at −78 °C. After 30 min hexachloroethane (4.93g, 20.81 mmol) in THF (12 mL) was added dropwise via a dropping funnel at −78 °C. The reaction mixture was stirred for 15 min and then quenched with saturated aqueous ammonium chloride (20 mL). After extraction with ethyl acetate (125 mL), the organic layer was separated, washed with water and brine, and dried over anhydrous sodium sulfate. After filtration, the solvents were evaporated under reduced pressure, and the resulting crude product was subjected to silica gel purification (8:2 hexanes:EtOAc). **1f** was obtained in 84.7% yield (3.18g, 17.63 mmol). Analysis data are in accordance with previously disclosed substrate.

*2-Chloro-1-(ethoxymethyl)-4-methyl-1H-imidazole (**4a**).* (1:1 regioisomeric mixture with 2-chloro-1-(ethoxymethyl)-5-methyl-1H-imidazole.)[17] NaH (60% dispersion in mineral oil) (9.74g, 244 mmol) was reacted with 4-methyl-1*H*-imidazole (5g, 60.90 mmol) in THF (70 mL) and chloromethyl ethyl ether (6.91g, 73.08 mmol) for 3 h at room temperature. After aqueous work up (NH_4Cl; chloroform), the crude product was purified by silica gel purification (9.5:0.5 chloroform/methanol), and an inseparable 1:1 mixture of 1-(ethoxymethyl)-4-methyl-1*H*-imidazole and 1-(ethoxymethyl)-5-methyl-1*H*-imidazole was obtained (5.9 g, 41.67 mmol, 64% yield). To the regioisomeric mixture (5.78g, 41.24 mmol) dissolved in THF (25 mL), *n*-BuLi (2.5 M in hexanes) (9.16gml, 22.89 mmol) was added at −78 °C. After 30 min, hexachloroethane (4.93g, 20.81 mmol) in THF (12 mL) was added dropwise at −78 °C. After 15 min, the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (125 mL). The organic layer was dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was subjected to silica gel purification (8:2 hexanes:EtOAc). **4a** was obtained in 89% yield (6.6 g, 36.67 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78−6.73 (m, 1H), 6.72−6.67 (m, 1H), 5.25 (s, 2H), 5.21 (s, 2H), 3.50 (q, J = 7.0 Hz, 4H), 2.29−2.23 (m, 3H), 2.21−2.15 (m, 3H), 1.24−1.15 (m,, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.0, 131.5, 131.0, 129.9, 126.0, 117.3, 75.2, 73.1, 64.5, 64.2, 14.9, 14.8, 13.9, 10.0. HRMS calcd for $C_7H_{11}ClN_2O$ $[M + H]^+$ 175.0633, found 175.0626.

*2-Chloro-1-(ethoxymethyl)-4-phenyl-1H-imidazole (**4b**).*[17] NaH (60% dispersion in mineral oil) (5.55g, 138 mmol) was reacted with 4-phenyl-1*H*-imidazole (5g, 34.68 mmol) in THF (70 mL) and chloromethyl ethyl ether (3.93g, 41.62 mmol) for 3 h at room temperature. After aqueous work up (NH_4Cl; chloroform), the crude

DOI: 10.1021/acs.joc.5b02592
J. Org. Chem. 2016, 81, 1269−1276

product was purified by silica gel purification (9.5:0.5 chloroform/methanol), and 1-(ethoxymethyl)-4-phenyl-1*H*-imidazole was obtained in 61% yield (4.3 g, 21.26 mmol). 1-(Ethoxymethyl)-4-phenyl-1*H*-imidazole (2.58g, 12.76 mmol) was dissolved in 8 ml THF and treated with *n*-BuLi (2.5 M in hexanes) (5.61 mL, 14.03 mmol) at −78 °C. After 30 min, hexachloroethane (3.02 g, 12.76 mmol) in THF (8 mL) was added dropwise at −78 °C. After 15 min, the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (125 mL). The organic layer was dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was subjected to silica gel purification (8:2 hexanes:EtOAc). **4b** was obtained in 63% yield (1.9 g, 8.03 mmol). ^{1}H NMR (400 MHz, MeOD) δ 7.72−7.68 (m, 2H), 7.67 (s, 1H), 7.40−7.33 (m, 2H), 7.28−7.22 (m, 1H), 5.39 (s, 2H), 3.59 (q, J = 7.0 Hz, 2H), 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.1, 1325, 132.4, 128.8, 127.7, 124.8, 116.2, 75.8, 64.9, 14.9. HRMS calcd for $C_{12}H_{13}ClN_2O$ $[M + H]^+$ 237.0789, found 237.0792.

*2-Chloro-4-(4-chlorophenyl)-1-(ethoxymethyl)-1H-imidazole (**4c**).*[17,19] 4-(4-Chlorophenyl)-1*H*-imidazole (3g, 16.80 mmol) in THF (36 mL) was reacted with NaH (60% dispersion in oil) (2.69g, 67.18 mmol) and chloromethyl ethyl ether (1.91g, 20.15 mmol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and 4-(4-chlorophenyl)-1-(ethoxymethyl)-1*H*-imidazole was obtained in 35% yield (1.4 g, 5.92 mmol). 4-(4-Chlorophenyl)-1-(ethoxymethyl)-1*H*-imidazole (1.4 g, 5.92 mmol) was dissolved in 6 mL THF and treated with TMPMgCl·LiCl (1 M in THF/toluene) (8.87 mL, 8.87 mmol) for 0.5 h at 0 °C and transferred via cannula to hexachloroethane (1.54g, 6.51 mmol) dissolved in 5.5 mL THF at −25 °C. After aqueous workup, the crude product was subjected to silica gel purification (8:2 hexanes:ethyl acetate), and **4c** was obtained in 63% yield (1.01g, 3.73 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.60 (m, 1H), 7.41−7.23 (m, 2H), 5.30 (s, 1H), 3.55 (q, J = 7.0 Hz, 1H), 1.22 (t, J = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.3, 132.9, 132.7, 131.5, 128.8, 125.9, 116.2, 75.6, 64.8, 14.8. HRMS calcd for $C_{12}H_{12}Cl_2N_2O$ $[M + H]^+$ 271.0399, found 271.0408.

*2-Chloro-1-(ethoxymethyl)-4-(4-fluorophenyl)-1H-imidazole (**4d**).*[17,19] 4-(4-Fluorophenyl)-1*H*-imidazole (3g, 18.50 mmol) in THF (36 mL) was reacted with NaH (60% dispersion in oil) (2.96g, 74.00 mmol) and chloromethyl ethyl ether (2.1 g, 22.20 mmol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and 4-(4-fluorophenyl)-1-(ethoxymethyl)-1*H*-imidazole was obtained in 43% yield (1.8 g, 7.95 mmol). 4-(4-Fluororophenyl)-1-(ethoxymethyl)-1*H*-imidazole (1.8 g, 7.95 mmol) was dissolved in 10 mL THF and treated with TMPMgCl·LiCl (1 M in THF/toluene) (11.92 mL, 11.92 mmol) for 0.5 h at 0 °C and transferred via cannula to hexachloroethane (5.64g, 23.84 mmol) dissolved in 24 mL THF at −25 °C. After aqueous workup, the crude product was subjected to silica gel purification (8:2 hexanes:ethyl acetate), and **4d** was obtained in 73% yield (1.47g, 5.77 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.67 (m, 2H), 7.28 (s, 1H), 7.06 (t, J = 8.7 Hz, 2H), 5.31 (s, 2H), 3.56 (d, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2 (d, J = 246.2 Hz), 140.7, 132.6, 129.2 (d, J = 3.0 Hz), 126.4 (d, J = 8.0 Hz), 115.7−115.5 (m), 75.6, 64.8, 14.8. HRMS calcd for $C_{12}H_{12}ClFN_2O$ $[M + H]^+$ 255.0695, found 255.0695.

*1-(Ethoxymethyl)-2-phenyl-1H-imidazole (**4e**).*[17] 2-Phenyl-1*H*-imidazole (3g, 20.81 mmol) in THF (40 mL) was reacted with NaH (60% dispersion in oil) (3.33g, 83.23 mmol) and chloromethyl ethyl ether (2.36g, 24.97 mmol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and **4e** was obtained in 75% yield (3.16g, 15.61 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.74 (m, 2H), 7.50−7.41 (m, 3H), 7.14 (dd, J = 6.8, 1.4 Hz, 2H), 5.29 (s, 2H), 3.55 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.6, 130.3, 129.0, 128.9, 128.7, 128.6, 121.5, 75.8, 64.4, 14.9. HRMS calcd for $C_{12}H_{14}N_2O$ $[M + H]^+$ 203.1179, found 203.1187.

*2-(4-Chlorophenyl)-1-(ethoxymethyl)-1H-imidazole (**4f**).*[17] 2-(4-Chlorophenyl)-1-(ethoxymethyl)-1*H*-imidazole (2g, 11.20 mmol) in THF (40 mL) was reacted with NaH (60% dispersion in oil) (1.79g, 44.79 mmol) and chloromethyl ethyl ether (1.27g, 13.44 mmol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and **4f** was obtained in 84% yield (2.21g, 9.34 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 6.2 Hz, 1H), 5.27 (s, 1H), 3.57 (q, J = 7.0 Hz, 1H), 1.24 (t, J = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.6, 135.1, 130.2, 128.9, 128.8,128.8, 122.0, 75.8, 64.6, 14.9. HRMS calcd for $C_{12}H_{13}ClN_2O$ $[M + H]^+$ 237.0789, found 237.0799.

*1-(Ethoxymethyl)-2-(4-fluorophenyl)-1H-imidazole (**4g**).*[17] 2-(4-Fluorophenyl)-1-(ethoxymethyl)-1*H*-imidazole (1g, 6.17 mmol) in THF (12 mL) was reacted with NaH (60% dispersion in oil) (0.99g, 24.67 mmol) and chloromethyl ethyl ether (0.7 g, 7.40 mmol) for 3 h at room temperature. After aqueous workup with chloroform and NH_4Cl, the reaction mixture was subjected to silica gel purification (9.5:0.5 chloroform/methanol), and **4g** was obtained in 75% yield (1.02g, 4.63 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.76 (m,, 1H), 7.18−7.11 (m, 2H), 5.26 (s, 1H), 3.57 (q, J = 7.0 Hz, 1H), 1.23 (t, J = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5 (d, J = 249.0 Hz), 147.8, 131.0, 130.9, 128.7, 126.5 (d, J = 3.4 Hz), 121.7, 115.8, 115.7, 75.9, 64.6, 15.0. HRMS calcd for $C_{12}H_{13}FN_2O$ $[M + H]^+$ 221.1085, found 221.1094.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02592.

Data regarding the evaluation of various fluorination reagents, copies of ^{1}H and ^{13}C NMR spectra for compounds **1a−c**, **3a−d**, **4a−g**, **5a−g**, and **6a−d**, and copies of ^{19}F NMR spectra of compounds **3a−d**, **5a−g**, and **6a−d** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank Dr. Jiejun Wu and Mrs. Heather McAllister for analytical support.

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