An Unusual Trifluoromethyl Elimination Reaction from the 4,4-Bis(trifluoromethyl)-5-hydroxyimidazoline Ring System

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A facile detrifluoromethylation was observed when 4,4-bis(trifluoromethyl)-5-hydroxyimidazoline **5** was treated with a variety of bases to afford the biologically interesting 4-(trifluoromethyl)-imidazole analogs (**9** and **10**). A unique mechanism was proposed for this transformation, supported by isolating and trapping the hypothesized intermediates. Heating of **5** with Et_4NCN in DMSO provided **19**, which was clearly derived from the proposed intermediate **17**. Finally, imidazole **9** was converted into the *N*-[2-phenyl-4-(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide analogs, which were potential acyl CoA:cholesterol acyltransferase (ACAT) inhibitors.

Introduction

Recently, we reported the synthesis of a series of 4,4-bis(trifluoromethyl)imidazolines (**1**) as potent acyl CoA: cholesterol acyltransferase (ACAT) inhibitors and/or cholesterol biosynthesis inhibitors.[3−7] These activities may be useful in the development of new agents for the treatment of hypercholesterolemia and atherosclerosis. During our efforts to synthesize 5-ester substituted 4,4-bis(trifluoromethyl)imidazoline analogs (**2**) as part of the structure−activity relationship (SAR) study,[6] we realized that the alcohol **5** was very labile to bases. One of the reactions we observed was an apparent detrifluoromethylation reaction, which converted the 4,4-bis(trifluoromethyl)imidazoline ring system to the 4-(trifluoromethyl)imidazole ring system. It is known that the trifluoromethyl group is one of the most stable functional groups and almost all the 4,4-bis(trifluoromethyl)imidazoline derivatives we have synthesized[3−7] so far appear to be very stable, both chemically and thermally. We disclose herein the reactions of the alcohol **5** with a variety of bases to give the biologically interesting 4-(trifluoromethyl)imidazole analogs.[8−15] A reaction mechanism was proposed for this transformation, which was supported by isolating and trapping the hypothesized intermediates.

Results and Discussions

The alcohol **5** was prepared as shown in Scheme 1. Treatment of the amidine **3** with wet alumina afforded the lactam **4** in surprisingly quantitative yield.[16] Alternatively, lactam **4** could be prepared from acylimine **6**, which was readily prepared from hexafluoroacetone and *p*-fluorobenzamide.[17] Addition of KCN to **6** afforded **7** in 65% yield.[18] The compound **7** existed as an equilibrium mixture between the cyano form and the *cis* and *trans* imidates as observed by the ^{1}H NMR spectrum.[19] Subsequently, **7** was converted to the lactam **8** with H_2O_2/NaOH in aqueous methanol[20] in one step with moderate yield. Methylation of **8** with CH_3I/NaH produced **4** in 76% yield. Dibal-H reduction of lactam **4** provided imidazoline alcohol **5** in quantitative yield.

Treatment of the alcohol **5** with sodium hydroxide or potassium hydroxide in DMSO afforded the imidazole **9** in moderate yields (Table 1). The structure of **9** was confirmed by X-ray crystal structure analysis (Figure 1). When non-hydroxide bases, such as *n*-Bu_4NF or K_2CO_3, were used, 5-fluoroimidazole **10** was also isolated as a minor product accompanying the major product **9**.

There are few cases in which a trifluoromethyl group is eliminated.[21,22] The transformation of **5** to **9** and **10** is a very unusual apparent detrifluoromethylation reaction with a net loss of CF_3OH or CF_2HOH. We propose here that the transformation of **5** to **9** goes through an

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Scheme 1

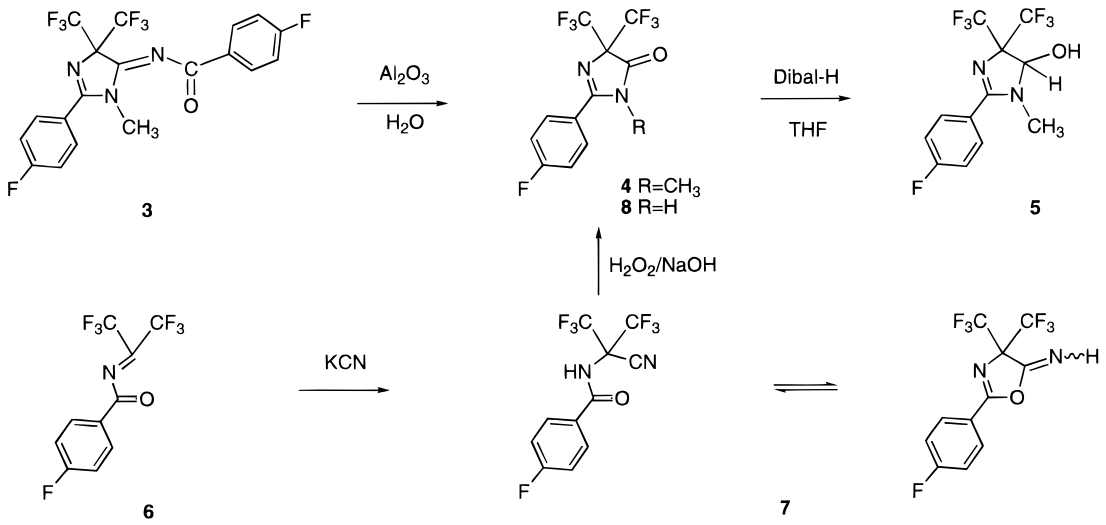
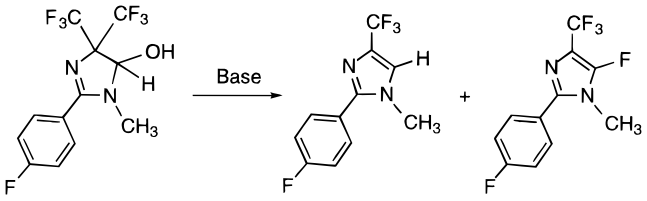


Table 1. Base-Promoted Conversion of 5 to 9 and 10



	reaction conditions				% yield of products[d]	
no.	base[a]	solvent[c]	temp (°C)	time (h)	**9**	**10**
1	NaOH (powder)	DMSO	120	2	51	
2	NaOH (powder)	DMSO	23	16	47	
3	NaOH (50% aqueous)	DMSO	120	2	39	
4	KOH (powder)	DMSO	23	16	55	
5	CsF	DMSO	120	2	62[e]	6
6	KF	DMSO	120	16	50	28
7	NaF	DMSO	120	16	20	trace
8	LiF	DMSO	120	16	11	trace
9	Bu_4NF[b]	THF	70	16	45[e]	13[e]
10	K_2CO_3	DMSO	120	4	60	7

[a] 10 equiv of bases were used. [b] 15 equiv was used. [c] All solvents were anhydrous and purchased from Aldrich Chemical Co. [d] Yields were determined by HPLC except when indicated. [e] Isolated yields.

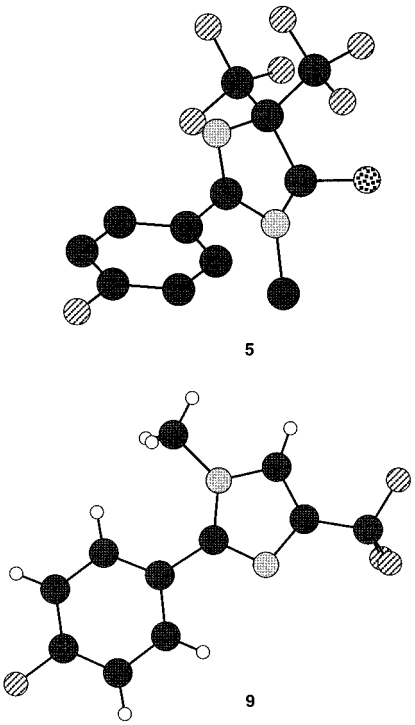


Figure 1. X-ray crystal structures of **5** and **9** (from Chem 3D based on their PDB files).

unprecedented difluorooxetane intermediate **14**, which loses carbonyl difluoride to form imidazole **9**. Difluorooxetane **14** could be formed through a ring-opening and ring-closure process through intermediates **12** or **13**, as shown in Scheme 2. Although α-hydroxylamines and *N*-acylhydroxylamines were known to exist in an equilibrium between aldehydes and amines or amides,[23,24] a few exceptions with carbonyl/α-carbon cleavage were also reported.[8,25,26] We believe that the *gem*-trifluoromethyl groups facilitated this carbonyl/α-carbon cleavage (i.e. **5** → **15**) both sterically and electronically.

It is unlikely that **14** was formed by an intramolecular displacement of fluoride from one of the trifluoromethyl groups by oxygen anion,[27−29] despite the fact that the hydroxyl group was very close to its *cis*-trifluoromethyl group in the X-ray crystal structure (Figure 1). We also considered the possibility of hydrolysis of vinyl fluoride **13** to carboxylic acid, which might undergo decarboxylation. This possibility was excluded by using CsF or K_2CO_3 as a base because very little water was presented in these reaction mixtures.

The ring-opened intermediates **12** or **15** could also be used to explain the formation of 5-fluoroimidazole **10**. Hydrolysis of formamide **15** should provide **16**, which could lose HF to give vinyl fluoride **17**. Subsequent ring closure of **17** followed by the fluoride elimination should provide the product **10**.[30,31] Burger reported[32] an analo-

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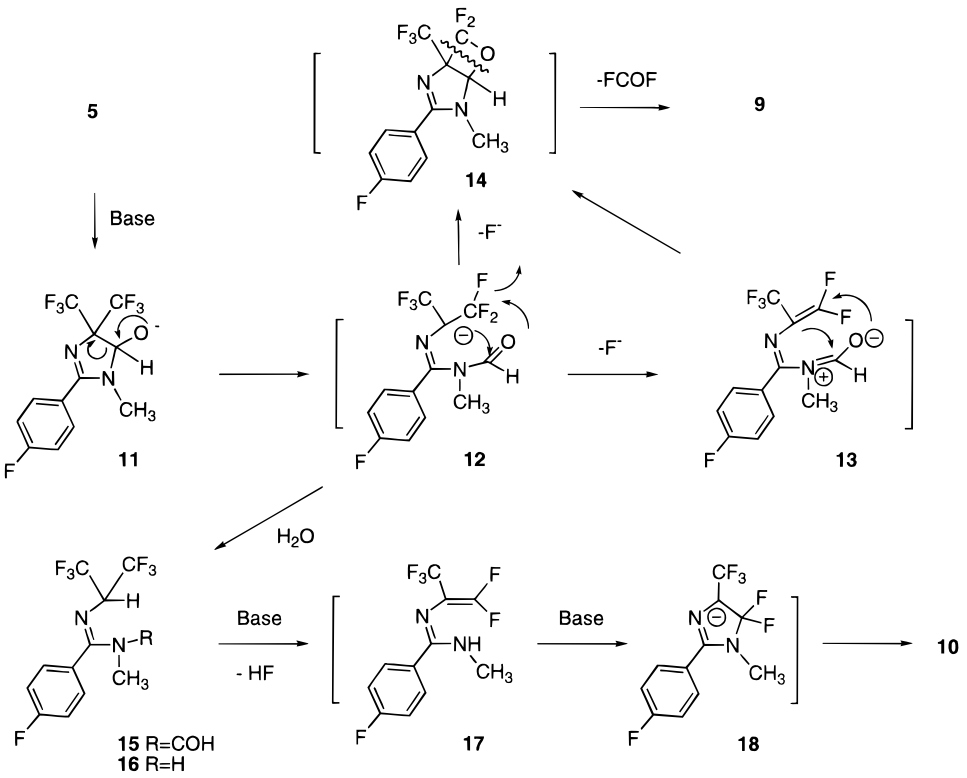
Scheme 2



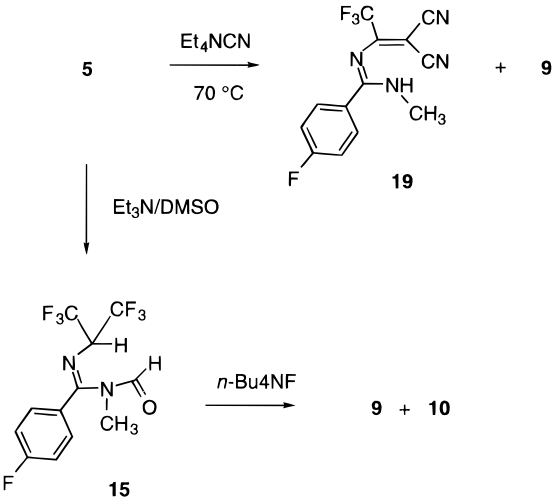
gous synthesis of 2-aryl-4-(trifluoromethyl)-5-fluoroimidazole by the reduction of the *N*-arylbenzamidines and hexafluoroacetone adducts with stannous chloride to produce intermediates like **18**, which provided similar 5-fluoroimidazole analogs.

Compound **5** was stable upon heating (120 °C, 4 h) in the absence of base. Methyl ether of **5** did not react upon treatment with *n*-tetrabutylammonium fluoride under reflux. These experiments suggested that deprotonation of the hydroxyl group was crucial for ring opening. We proposed that further transformations require a base that could deprotonate **15** and **16**. Thus, if a base could only deprotonate **5**, but not **15** and **16**, the ring-opened compound **15** should be the reaction product. Heating of **5** with weaker bases, such as Et_3N, allowed us to isolate and characterize **15** (Scheme 3) in variable isolated yields. Treatment of **15** with *n*-tetrabutylammonium fluoride afforded a mixture of **9** and **10**, as expected.

Compounds resembling **17** have rarely been encountered. It is known, however, that vinyl fluoride can be displaced by a variety of nuclophiles, presumably through an addition and elimination mechanism.[30,33] Heating of **5** with Et_4NCN in DMSO at 70−90 °C provided **19**, which was clearly derived from **17**, as a major product (70%) along with small amount of **9**. Compound **19** was very stable with a unique and interesting structure.[34]

"Elimination" of a trifluoromethyl group of the *gem*-bis(trifluoromethyl) compounds such as **5** by a novel ring-opening and ring-closing mechanism provided a unique way to synthesize regioselectively trifluoromethyl-substituted heterocycles, which possessed very interesting biological activities. 4-(Trifluoromethyl)imidazole **9** was then converted to the amide analogs **22** and **23** (Scheme 4). Treatment of **9** with *n*-BuLi followed by 4-fluorobenzaldehyde gave alcohol **20**, which was subsequently oxidized by PCC to the ketone **21**. Schmidt rearrangement of **21** afforded two amides, **22** and **23**. For direct comparison with our previously synthesized imidazoline series of ACAT inhibitors, **23** was methylated to produce **24** in 95% yield. Both **23** and **24** showed moderate inhibition in our ACAT in vitro assay, which was comparable to the imidazoline series.[3−6]

Scheme 3



Experimental Section[35]

Preparation of 2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-4*H*-imidazol-5-one (4). A solution of *N*-[4,4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-

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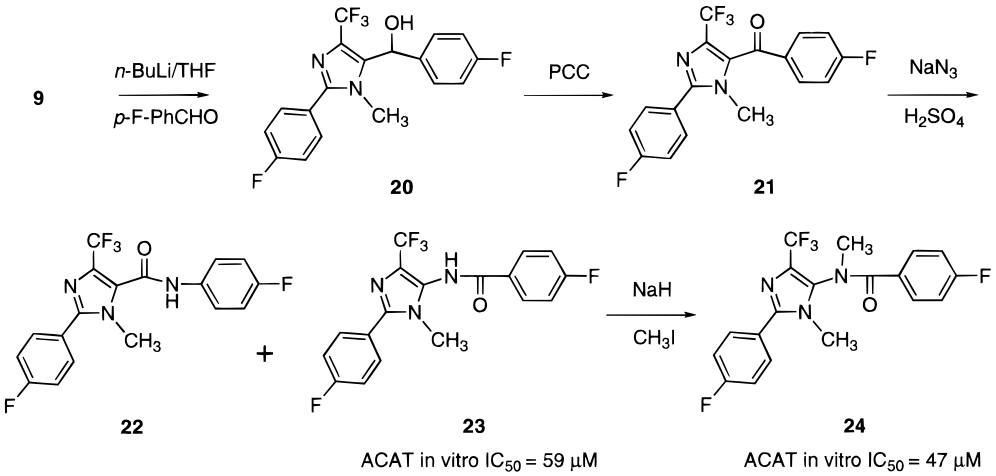
Scheme 4



1-methyl-1*H*-imidazol-5-ylidene]-4-(fluorophenyl)benzamide (**3**)[3] (1.1 g, 2.3 mmol) in diethyl ether was eluted to the center of a basic alumina (III) column with diethyl ether at room temperature. After 2 h, the material was eluted from the column with ethyl acetate and the crude product was purified by column chromatography with hexane−ethyl acetate (10:1) to give the title compound **4** in quantitative yield (0.80 g, 100%) as a white solid: mp 59−61 °C; IR (KBr) 1767, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.28 (s, 3H, NCH_3), 7.27 (t, J = 8.8 Hz, 2H), 7.78 (dd, J = 5.1, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −72.17 (s, 6F, 2 × CF_3), −105.12 (m, 1F); MS *m*/*e* 329 $(M + H)^+$; HRMS for $C_{12}H_7F_7N_2O$ (M^+) calcd 328.0447, found 328.0454. Anal. Calcd for $C_{12}H_7F_7N_2O$ C, 43.92; H, 2.15; N, 8.54; F, 40.52. Found: C, 43.91; H, 1.80; N, 8.48; F, 40.36.

Preparation of *N*-[1-Cyano-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-4-fluorobenzamide and 2-(4-Fluorophenyl)-4,4-bis(trifluoromethyl)-5(4*H*)-oxazolimine (7). To a solution of 4-fluoro-*N*-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]benzamide (**6**)[18,19] (72.7 g, 0.25 mol) in anhydrous diethyl ether (145 mL) was added KCN (22.0 g, 0.34 mol) at 0 °C in portions. After stirring at room temperature overnight, the reaction mixture was worked up to give the title compound (**7**) (53.2 g, 65%) as a crystalline solid. This product exists as an equilibrium of three compounds in chloroform: mp 127−128 °C; IR (KBr) 3268, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 0.21H, NH), 7.19−7.26 (m, 2H), 7.84 (dd, J = 5.3, 8.7 Hz, 0.42H), 8.10 (dd, J = 5.3, 8.7 Hz, 0.84H), 8.17 (dd, J = 5.3, 8.7 Hz, 0.74H), 8.74 (s, 0.42H, NH), 9.28 (s, 0.37H, NH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.02 (s, 1.2F, CF_3), −73.52 (s, 2.5F, CF_3), −73.58 (s, 2.3F, CF_3), −102.11 (m, 0.38F), −102.32 (m, 0.42F), −104.01 (m, 0.20F); MS *m*/*e* 315 $(M + H)^+$; HRMS for $C_{11}H_6F_7N_2O$ $(M + H)^+$ calcd 315.0368, found 315.0368. Anal. Calcd for $C_{11}H_5F_7N_2O$ C, 42.06; H, 1.60; N, 8.92. Found: C, 41.94; H, 1.73; N, 8.89.

Preparation of 2-(4-Fluorophenyl)-4,5-dihydro-4,4-bis-(trifluoromethyl)-4*H*-imidazol-5-one (8). To a solution of **7** (10.0 g, 31.9 mmol) in 10% NaOH (30 mL) and MeOH (30 mL) was added 30% H_2O_2 (30 mL) dropwise over 10 min at 0 °C. The reaction mixture was stirred at room temperature for another 2 h and neutralized with 1 N HCl to pH 7. The mixture was concentrated in vacuo to remove most of the methanol. After dilution with water (100 mL), the aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium sulfite twice and saturated aqueous sodium chloride twice, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was crystallized from ethyl acetate and hexane to give the title compound (**8**, 4.7 g, 47%) as a white crystalline solid: mp 152−154 °C; IR (KBr) 3302, 1771, 1628 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H, NH), 8.07 (dd, J = 5.3, 8.7 Hz, 2H), 7.28 (t, J = 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −71.86 (s, 6F), −102.85 (m, 1F); HRMS for $C_{11}H_6F_7N_2O$ $(M + H)^+$ calcd 315.0368, found 315.0346. Anal. Calcd for $C_{11}H_5F_7N_2O$ C, 42.06; H, 1.60; N, 8.92. Found: C, 43.91; H, 1.21; N, 9.12.

Preparation of 2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-4*H*-imidazol-5-one (4). Sodium hydride (60% suspension in mineral oil, 1.73 g, 26 mmol) was suspended in anhydrous dimethylformamide (25 mL). To this suspension was added a solution of **8** (5.77 g, 18.4 mmol) in anhydrous DMF (25 mL) dropwise at 0 °C. The resulting reaction mixture was allowed to stir at room temperature for 30 min before iodomethane (3.65 g, 26 mmol) was added dropwise. After being stirred at room temperature for 2 h, the reaction mixture was poured into water and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was crystallized in hexane/ethyl acetate to give the title compound (**4**, 4.6 g, 76%), which was identical with the authentic sample obtained above.

Preparation of 2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-ol (5). To a solution of 2-(4-fluorophenyl)-3,5-dihydro-3-methyl-4,4-bis-(trifluoromethyl)-4*H*-imidazol-4-one (**4**) (1.21 g, 3.69 mmol) in anhydrous THF (40 mL) was added a DIBAL-H solution (1.0 M in THF, 5 mL, 5 mmol) over 10 min. After being refluxed for 2 h under nitrogen, the reaction mixture was quenched with methanol (0.5 mL) and water (300 mL). The mixture was extracted with diethyl ether (2 × 50 mL) and then ethyl acetate (2 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the title compound (**5**) as a white crystalline solid (1.209 g, 100%): mp 180−195 °C; IR (KBr) 1606, 1564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (d, J = 9.5 Hz, 1H), 3.02 (s, 3H, NCH_3), 5.48 (d, J = 9.5 Hz, 1H), 7.16 (t, J = 8.7 Hz, 2H), 7.62 (dd, J = 5.3, 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −68.83 (q, J = 9.5 Hz, 3F, CF_3), −76.65 (q, J = 9.5 Hz, 3F, CF_3), −107.98 (m, 1F); HRMS for $C_{12}H_9F_7N_2O$ (M^+) calcd 330.0603, found 330.0603.

General Procedure for Reaction of 2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-ol (5) with Bases. Compound **5** (1 equiv) and a base (5−10 equiv) were mixed in anhydrous DMSO, and the reaction mixture was heated at 120 °C for 4−24 h. After cooling to room temperature, the reaction was quenched with water and extracted with diethyl ether or ethyl acetate. The combined organic layers were washed successively with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography.

Preparation of 2-(4-Fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole (9). This compound was obtained from **5** (50 mg, 0.15 mmol) and CsF (229 mg, 1.5 mmol) following the general procedure described above in 62% as a white crystalline solid: mp 86−87.2 °C; IR (KBr) 3126, 2960, 1610, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, NCH_3), 7.19 (t, J = 8.5 Hz, 2H), 7.30 (s, 1H), 7.61 (dd, J = 5.5,

8.5 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −63.279 (s, 3F, CF_3), −111.363 (m, 1F); HRMS for $C_{11}H_9F_4N_2$ $(M + H)^+$ calcd 245.0702, found 245.0706. Anal. Calcd for $C_{11}H_8F_4N_2$ C, 54.11; H, 3.30; N, 11.47. Found: C, 53.93; H, 3.13; N, 11.33.

Preparation of 2-(4-Fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole (9) and 5-Fluoro-2-(4-fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole (10). To a solution of **5** (108 mg, 0.33 mol) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 5 mL, 5 mmol) and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the reaction was quenched with water (50 mL) and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to afford three fractions: I (12 mg), II (11 mg, 13%), and III 36 mg (**9**, 45%). Fraction II was the title compound (**10**): IR (KBr) 2964, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (d, J = 0.8 Hz, NCH_3), 7.11 (t, J = 8.7 Hz, 2H), 7.53 (dd, J = 4.9, 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −62.08 (d, J = 10.3 Hz, 3F), −110.67 (m, 1F), −141.50 (q, J = 10.3 Hz, 1F), HRMS for $C_{11}H_8F_5N_2$ (M^+) calcd 263.0608, found 263.0605.

Preparation of 4-Fluoro-*N*-formyl-*N*-methyl-*N*′-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzenecarboximidamide (15). The mixture of **5** (246 mg, 0.75 mmol) and Et_3N (2 mL, 27 mmol) in anhydrous DMSO (3 mL) was heated at 100 °C for 24 h. After cooling to room temperature, the reaction was quenched with water (40 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed successively with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography to give the recovered starting material **5** (160 mg) and the title compound **15** as a viscous oil (12 mg, 14%): IR (KBr) 1720, 1708, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.27 (m, 4H), 4.06 (m, 1H), 3.35 (s, 3H, NCH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −107.40 (m, 1F), −71.65 (d, J = 6.9 Hz, 6F); HRMS for $C_{12}H_8F_7N_2O$ $(M + H)^+$ calcd 329.0525, found 329.0529.

Preparation of *N*′-[2,2-Dicyano-1-(trifluoromethyl)-ethenyl]-4-fluoro-*N*-methylbenzenecarboximidamide (19). To a solution of **5** (1.53 g 4.56 mmol) in anhydrous DMSO (15 mL) was added Et_4NCN[36] (3.02 g, 18 mmol) at 70 °C over 2 h. After it was stirred at 70 °C for another 14 h and then cooled to rt, the reaction mixture was poured into water (300 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to give the compound **9** (142 mg, 13%) and the title compound (**19**, 947 mg, 70%) as a crystalline solid: mp >250 °C; IR (KBr) 3350, 2373, 1617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (d, J = 7.5 Hz, 3H, NCH_3), 7.34 (m, 2H), 7.74 (br s, 1H, NH), 8.57 (m, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.450 (s, 3F, CF_3), −109.554 (m, 1F); HRMS for $C_{13}H_9F_4N_4$ $(M + H)^+$ calcd 297.0763, found 297.0771.

Preparation of *N*,2-Bis(4-fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole-5-carboxamide (22) and 4-Fluoro-*N*-[2-(4-fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (23). To a solution of **9** (525 mg 2.15 mmol) in anhydrous THF (20 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 1.47 mL, 2.3 mmol) dropwise at −70 °C. After the reaction mixture was stirred at −78 °C for 2 h, a solution of 4-fluorobenzaldehyde (267 mg, 2.15 mmol) in THF (5 mL) was added slowly. The resulting reaction mixture was stirred at −78 °C for 1 h and then at 23 °C for another 1 h. The reaction was quenched with aqueous saturated ammonium chloride solution (40 mL) and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and reacted with PCC (1.1 g, 5.1 mmol). The resulting reaction mixture was stirred at room temperature for overnight, diethyl ether (30 mL) was added, and the solvent was decanted. The solid was washed with diethyl ether twice. The combined diethyl ethereal solution was purified by a short Florisil column. The solvent was removed under reduced pressure to give a residue (**21**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H, NCH_3), 7.21 (t, J = 8.7 Hz, 2H), 7.23 (t, J = 8.7 Hz, 2H), 7.68 (dd, J = 5.3, 8.7 Hz, 2H), 7.96 (dd, J = 5.3, 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −59.71 (s, 3F, CF_3), −102.83 (m, 1F), −109.83 (m, 1F). The residue was dissolved in benzene (10 mL) and concd H_2SO_4 (4 mL). To this solution, was added NaN_3 (264 mg, 4 mmol) in portions at <5 °C. The reaction mixture was stirred at 0 °C for 2 h and then room temperature for 2 days. After the reaction mixture was quenched with ice, the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to give compounds **22** (96 mg, 27%) and **23** (248 mg, 70%). For **22**: mp 183−184 °C; IR (KBr) 3251, 1672, 1612, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, NCH_3), 7.08 (t, J = 8.4 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 7.53−7.62 (m, 4H), 8.11 (br s, 1H, NH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −59.348 (s, 3F, CF_3), −109.853 (m, 1F), −116.548 (m, 1F); HRMS for $C_{18}H_{12}F_5N_3O$ (M^+) calcd 381.0901, found 381.0904; For **23**: mp 114−116 °C; IR (KBr) 3258, 1672, 1666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H, NCH_3), 7.19 (t, J = 8.7 Hz, 2H), 7.23 (t, J = 8.3 Hz, 2H), 7.66 (m, 3H), 7.95 (dd, J = 5.3, 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −61.855 (s, 3F, CF_3), −105.493 (m, 1F), −111.02 (m, 1F); HRMS for $C_{18}H_{12}F_5N_3O$ (M^+) calcd 381.0901, found 381.0900.

Preparation of 4-Fluoro-*N*-[2-(4-fluorophenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (24). To a suspension of sodium hydride (60% suspension in mineral oil, 29 mg, 0.72 mg) in anhydrous dimethylformamide (5 mL) was added in portions **23** (230 mg, 0.6 mmol) and the mixture was allowed to stir at room temperature for 30 min. Iodomethane (103 mg, 0.72 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the title compound (**24**, 226 mg, 95%): mp 123−125 °C; IR (KBr) 2924, 1671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3H, NCH_3), 3.44 (s, 3H, NCH_3), 6.97 (t, J = 8.4 Hz, 2H), 7.16 (t, J = 8.4 Hz, 2H), 7.37 (m, 2H), 7.48 (m, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −63.194 (s, 3F, CF_3), −108.034 (m, 1F), −110.289 (m, 1F); HRMS for $C_{19}H_{14}F_5N_3O$ (M^+) calcd 395.1057, found 395.1072.

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Supporting Information Available: ^{1}H NMR and ^{19}F NMR spectra for compounds **4**, **5**, **7**−**10**, **15**, **19**, **21**, and **22**−**24** and the X-ray crystal structure data for **5** and **9** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(36) The purity of this material is 94% from Aldrich Chemical Co.

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