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Supporting Information

For

Development of a Telescoped Synthesis of 4-(1H)-Cyanoimidazole Core Accelerated by Orthogonal Reaction Monitoring

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Contents

General Remarks

Reagents

4-methylbenzaldehyde was purchased from Sigma Aldrich and used as received. 3,3-dibromo-1,1,1-trifluoropropan-2-one was purchased from Oakwood Chemicals and used as received. Ammonium Hydroxide (28 wt %) was purchased form VWR and used as received. NaOH was purchased from Fischer and used as received. All other reagents and solvents were purchased from conventional suppliers and used as received unless otherwise stated. Silica gel was purchased from Silicycle (60 Å, 230 x 400 mesh).

Analytical Methods

NMR spectra were recorded on a Bruker AV-400 for ^{1}H, ^{13}C, and ^{19}F and were referenced to the residual solvent peak.[1] The abbreviations s, d, q, m signify singlet, doublet, quartet, and multiplet, respectively. NMR spectra were analyzed by using the software MNova.

The Liquid Chromatography (LC) samples were analyzed by HPLC/MS conducted on an Agilent 1200 HPLC with the following configuration:

Agilent G1379B degasser, G1312A binary pump, G1316A thermal column compartment, diode array detector and a 6120 single quad mass spectrometer.

Analytical setting for the detectors are:

DAD – 200 – 400 nm collected at 20 Hz storing all spectra for offline analysis. Peak area for quantification varies depending on the experiment, see calibration curves for details

ESI-MSD – positive mode scan for m/Z 110 – 1500 running at 0.8sec/cycle. drying gas = 7.0 l/min, nebulizer pressure = 20 psi, gas temperature = 300 °C, capillary voltage = 4000 V

HPLC column and mobile phase method used the follow conditions:

(1) Poroshell C18, 2.1 x 50 mm, 2.7-Micron Column; Temperature = 25 ºC;
Solvent A = Water, 0.1 % Formic Acid; Solvent B = acetonitrile; Flow Rate = 0.650 mL/min; Starting Conditions = 90 % A, 10 % B; 0.0 - 0.8 min isocratic; 0.8 – 3.5 min gradient to 10% A, 90 % B

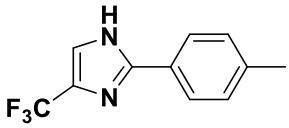
(2) Poroshell C18, 2.1 x 50 mm, 2.7-Micron Column; Temperature = 25 ºC;
Solvent A = Water, 0.1 % Formic Acid; Solvent B = acetonitrile; Flow Rate = 0.650 mL/min; Starting Conditions = 99 % A, 1.0 % B; 0.0 - 2.00 min gradient to 80% A, 20 % B; 2.0 – 3.0 min gradient to 0.0% A, 100 % B.

Instrumentation

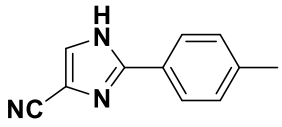
Experiments were performed in a Mettler-Toledo Easymax 102 Advanced Synthesis Workstation. Temporal HPLC data was obtained using an automated reaction sampling platform similar to what was previously reported in our group.[2-4]

All commands were executed by Trilution software working in conjunction with a Gilson Liquid Handler. At fixed time points, ~20 µL samples were automatically taken via the Easysampler probe. Methanol (1.00 mL) was used to deliver through the reaction aliquot into a vial for subsequent HPLC analysis. The sampling lines were then flushed with nitrogen gas for 2 minutes before reinitiating the sampling sequence.

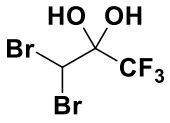
Synthetic Procedures and Characterization Data



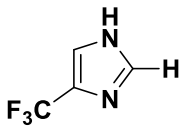
2-(*p*-tolyl)-4-(trifluoromethyl)-1*H*-imidazole (3):
4-methylbenzaldehyde (300 mg, 2.50 mmol) was added to a flask containing 2-propanol (10 mL) and aqueous (28 wt %) ammonium hydroxide (3.5 mL, 25.0 mmol). 3,3-dibromo-1,1,1-trifluoropropan-2-one (1.35 g, 5.0 mmol) was hydrated by adding to water (1.0 mL) slowly and the resulting aqueous solution was then transferred into the reaction flask where it was then heated at 40 °C for six hours. The solvent was removed under reduced pressure and the resulting crude was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. After the solvent was evaporated, the crude product was purified by column chromatography (petroleum ether/ethyl acetate 4:1) to afford imidazole **3** (435 mg, 1.92 mmol, 77% yield) as a white solid.
^{1}H NMR (400 MHz, MeOD) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.59 (q, *J* = 1.3 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 2.37 (s, 3H); **^{13}C NMR** (101 MHz, MeOD) δ 148.8, 139.7, 131.4 (q, *J* = 39.3, 37.4 Hz), 129.2, 126.3, 125.5, 122.0 (q, *J* = 265.8 Hz), 117.5, 19.9; **^{19}F NMR** (377 MHz, MeOD) δ -63.45. **HRMS** (EI-TOF) *m/z* calculated for $C_{11}H_9F_3N_2$, = 226.07178; found 226.07189.



2-(*p*-tolyl)-1*H*-imidazole-4-carbonitrile (4):
2-(*p*-tolyl)-4-(trifluoromethyl)-1H-imidazole (100 mg, 0.44 mmol) was added to 2-propanol (6.0 mL) and aqueous (28 wt %) ammonium hydroxide (6.1 mL, 4.4 mmol) and heated to 60 °C. Aqueous (10 M) sodium hydroxide (0.27 mL, 2.6 mmol) was added to the reaction in 6 equal portions over the course of 90 minutes. The reaction solution was neutralized with saturated-aqueous ammonium chloride and the isopropanol was removed under reduced pressure. The crude was extracted with ethyl acetate. The combined organic layers were washed with saturated ammonium bicarbonate solution, then brine, dried over $MgSO_4$. and concentrated under reduced pressure to afford **4** (71 mg, 0.44 mmol, 88% yield) as a tan solid.
^{1}H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H); **^{13}C NMR** (101 MHz, MeOD) δ 150.5, 141.5, 130.7, 128.9, 127.12, 126.9, 115.9, 113.8, 21.3; **HRMS** (EI-TOF) *m/z* calculated for $C_{11}H_9N_3$, $[M]^+$ = 183.07965; found 183.07944



3,3-dibromo-1,1,1-trifluoropropane-2,2-diol (6):
3,3-dibromo-1,1,1-trifluoropropan-2-one was hydrated by adding 3,3-dibromo-1,1,1-trifluoropropan-2-one (989 mg, 442 µL, 3.67 mmol) over the course of 15 minutes to distilled water (1.0 mL) in an ice bath while stirring to afford **6**.
^{1}H NMR (400 MHz, D_2O) δ 5.84; **^{13}C NMR** (101 MHz, D_2O) δ 121.4 (q, *J* = 289.9 Hz), 92.6 (q, *J* = 31.0 Hz), 43.7; **^{19}F NMR** (377 MHz, D_2O) δ -78.0.



4-(trifluoromethyl)-1*H*-imidazole (11):
Compound **11** was prepared as per the following procedure.[5]
^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.59 (p, J = 1.3 Hz, 1H); **^{13}C NMR** (101 MHz, MeOD) δ 136.9, 130.6 (q, *J* = 38.4 Hz), 121.9 (q, *J* = 265.5 Hz), 116.9; **^{19}F NMR** (377 MHz, MeOD) δ -63.34.[1] **HRMS** (EI-TOF) *m/z* calculated for $C_4H_3F_3N_2$, $[M]^+$ = 136.02483; found 136.02473.

Variable Time Course ^{19}F Experiments

Dimerization of 6 Experiments

Aqueous (28 wt%) ammonium hydroxide (0.17 mL, 1.2 mmol) was added to MeOD (400 µL) in an NMR tube sealed with a Teflon screw cap. The sample was placed in the NMR spectrometer where a preliminary ^{19}F spectrum was recorded. 3,3-dibromo-1,1,1-trifluoropropane-2,2-diol (72 mg, 0.27 mmol) in D_2O (66 µL) was added to the NMR tube to initiate the reaction. An NMR time-course experiment was initiated by obtaining a ^{19}F NMR spectrum at a rate of one spectrum every 75 seconds for a total of 56 spectra.

This experiment was then repeated but instead a temperature of 40 ºC was maintained in the spectrometer. A ^{19}F NMR spectrum was obtained at a rate of one spectrum every 75 seconds for a total of 56 spectra.

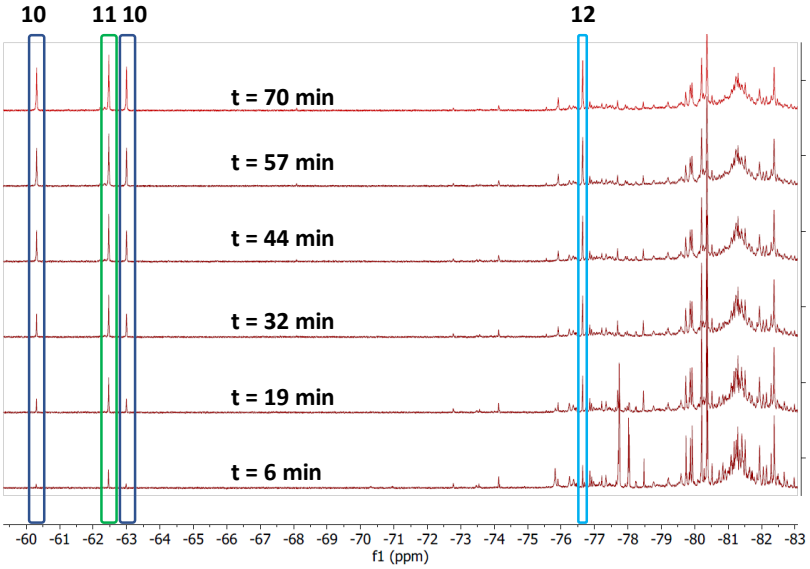
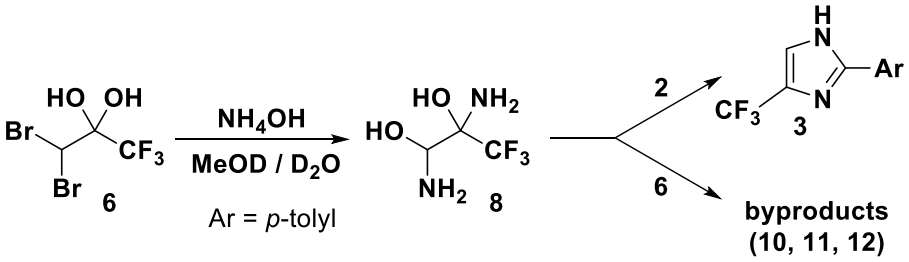


Figure S1: Time course ^{19}F spectra for the reaction of **6** in NH_4OH

Imidazole Forming Experiments



Aqueous (28 wt %) ammonium hydroxide (0.15 g, 0.17 mL, 1.2 mmol) was added to a solution of MeOD (400 µL) and 4-methylbenzaldehyde (16.2 mg, 16 µL, 0.135 mmol) in an NMR tube sealed with a Teflon screw cap. The sample was placed in the NMR spectrometer where a preliminary ^{19}F spectrum was recorded. 3,3-dibromo-1,1,1-trifluoropropane-2,2-diol (72 mg, 0.27 mmol) in D_2O (66 µL) was added to the NMR tube to initiate the reaction. An NMR time-course experiment was performed whereby a ^{19}F NMR spectrum was obtained at a rate of one spectrum every 240 seconds for a total of 160 spectra.

This experiment was then repeated but instead a temperature of 40 ºC was maintained in the spectrometer. A ^{19}F NMR spectrum was obtained at a rate of one spectrum every 59 seconds for a total of 175 spectra.

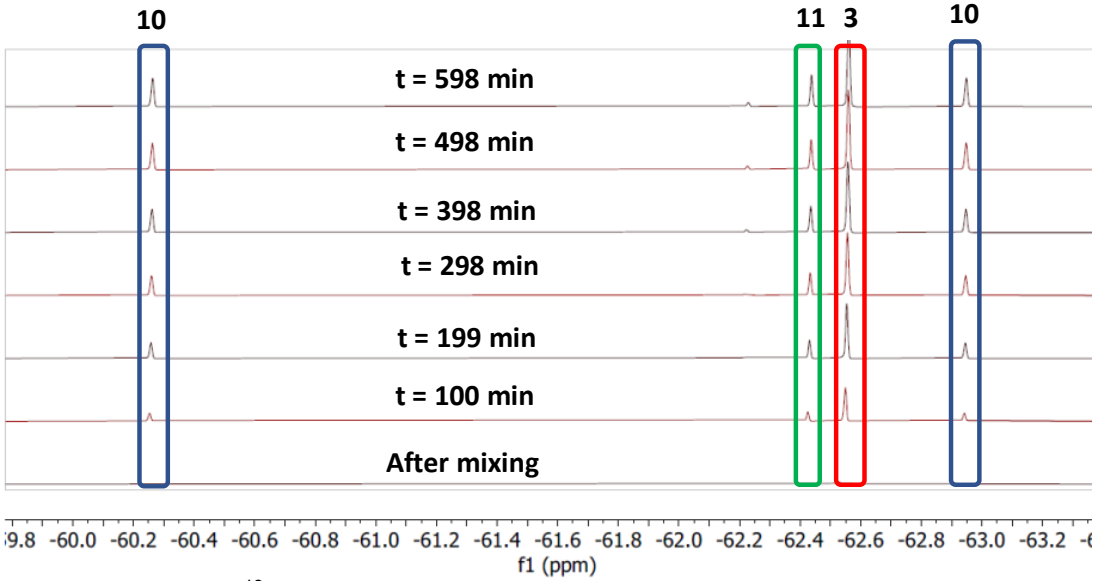


Figure S2: Time course ^{19}F spectra for the reaction of **2** and **6** in aqueous NH_4OH.

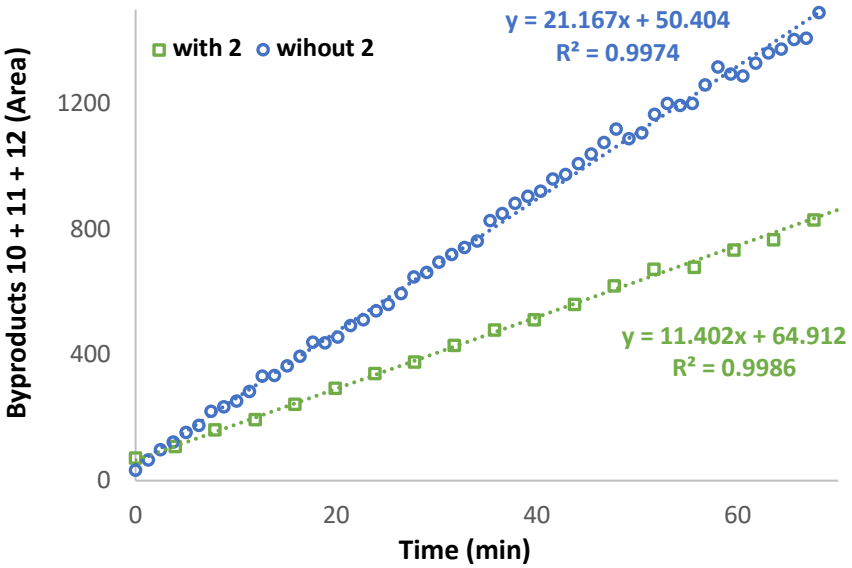
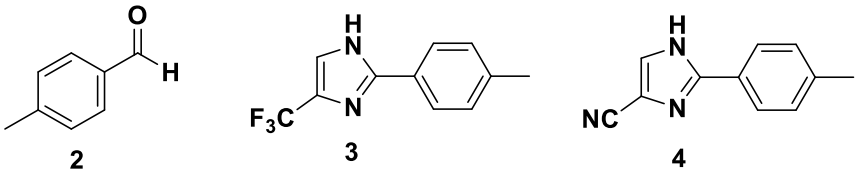


Figure S3: Time course ^{19}F spectroscopy data comparing the rates of formation of byproducts **10**, **11**, and **12** in the absence and presence of **2**.

Calibration Curves



2 3 4

A stock solution of each compound being calibrated (**2**, **3**, and **4**) was created by adding a known mass of material to 1.00 mL of methanol. This stock solution was then sampled three times using the Easysampler sampling method, and the peak areas were quantified using HPLC-method A. The stock solution (600 µL) was then added into methanol (400 µL) and the diluted stock solution was sampled again three times. This diluting and sampling protocol was repeated an additional two times.

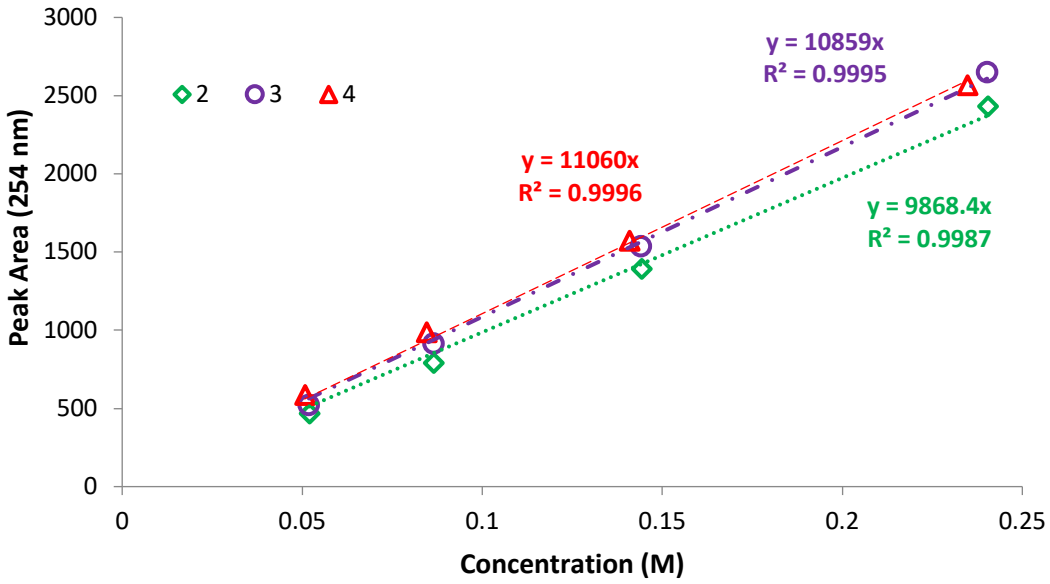
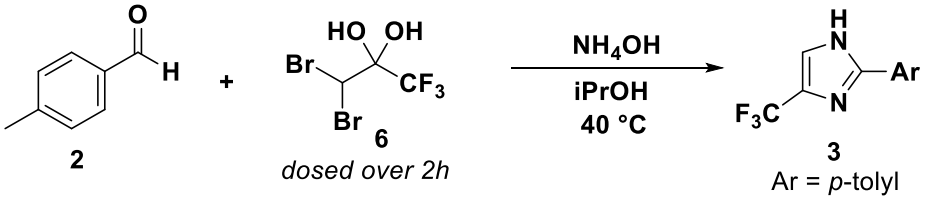


Figure S4: Calibration curve data for compounds **2**, **3**, and **4** with least-squares regression line of best fit. Peak areas were measured at 254 nm.

Dosing Experiments

Dosing Experiment 1



4-methylbenzaldehyde (400 mg, 3.33 mmol) was added to a solution of isopropanol (10 mL) and aqueous (28 wt%) ammonium hydroxide (2.8 mL, 20 mmol) and the temperature was increased to 40 °C. The ReactIR probe was blanked in air, then NH_4OH/IPrOH (4:1), and was inserted into the reaction flask. Data acquisition using iC IR (React IR software) was initiated recording one spectrum every two minutes. 3,3-dibromo-1,1,1-trifluoropropan-2-one (989 mg, 3.67 mmol) was hydrated by adding **1** slowly to distilled water (1 mL) in an ice bath with stirring. The aqueous solution of **6** was then dosed into the reaction flask over the course of 2 hours while maintaining a reaction temperature of 40 °C. Once dosing had begun a sampling sequence was initiated. ReactIR data analysis was performed on the double derivative of the IR spectra to allow for better peak deconvolution. Imidazole **3** was trended via the peak at 1357 cm^{-1}. HPLC samples were analyzed using HPLC method 1.

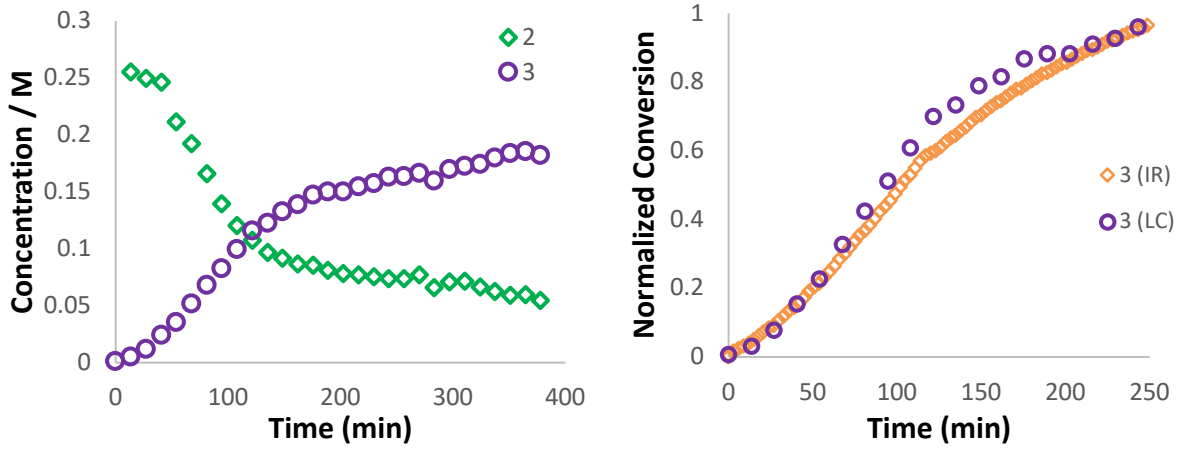
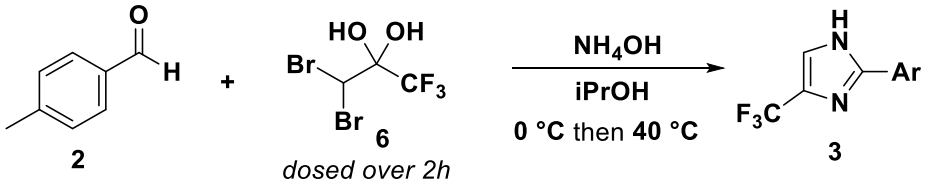


Figure S6: HPLC conversion profiles of **2** and **3** for dosing experiment 2 (left). Overlay of normalized conversion of **3** via FTIR and HPLC measurements.

Dosing Experiment 2



4-methylbenzaldehyde (400 mg, 3.33 mmol) was added to a solution of isopropanol (10 mL) and aqueous (28 wt %) ammonium hydroxide (2.8 mL, 20 mmol). The resulting solution was cooled to 0 °C while stirring. The ReactIR probe was blanked in air, then NH_4OH/IPrOH (4:1), and was inserted into the reaction flask. Data acquisition using iC IR (React IR software) was initiated recording one spectrum every two minutes. 3,3-dibromo-1,1,1-trifluoropropan-2-one (989 mg, 3.67 mmol) was hydrated by adding **1** slowly to distilled water (1.0 mL) in an ice bath while stirring. The aqueous solution of **6** was then dosed into the reaction flask over the course of 2 hours while maintaining a reaction temperature of 0 °C. A sampling sequence was initiated once dosing had begun. After 150 minutes the reaction temperature was increased to 40 °C. ReactIR data analysis was performed on the double derivative of the IR spectra to allow for better peak deconvolution. Imidazole **3** was trended via the peak at 1357 cm^{-1}. HPLC samples were analyzed using HPLC method 1.

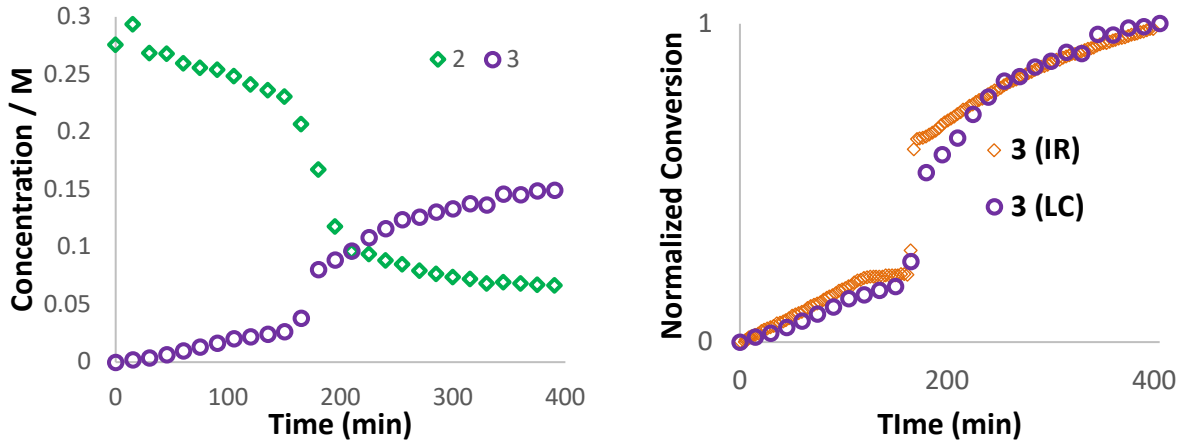


Figure S5: HPLC conversion profiles of **2** and **3** for dosing experiment 1 (left). Overlay of normalized conversion of **3** via temporal FTIR and HPLC measurements.

Design of Experiments

Reaction Experimental designs were formulated using the statistical software package JMP (SAS Institute) as custom designs. The DoE was run with 24 experiments including 4 center points and 5 factors using a D-Optimal design criteria as shown in Table S1. The experiments were blocked in groups of 3 based on reaction temperature.

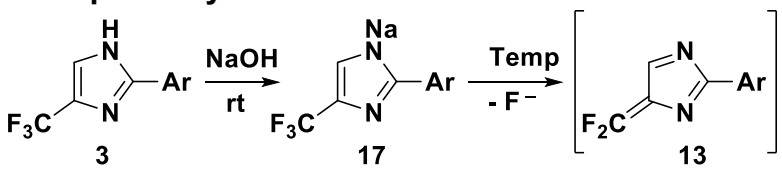
Procedures: At 0 °C, 4-methylbenzaldehyde was added to 8 mL vials followed by addition of aqueous (28 wt %) NH_4OH. Then, 1,1-dibromo-3,3,3-trifluoroacetone solution in isopropanol was added to the reaction mixture at 0 °C, followed by the addition of extra isopropanol or H_2O to achieve the desired IPA/water ratio and total volume. The vials were then transferred to a heating block at desired reaction temperature and stirred at 300 rpm.

Table S1: DoE for Imidazole Formation Step

	NH4OH equiv	Ketone equiv	Volumes	Temperature	Amount of Water (IPA:H2O)
A1	6	1.25	47	40	1.5
A2	18	2	41	40	1.5
A3	6	1.25	27	40	1.5
A4	6	2	47	40	1.5
A5	18	2	61	40	1.5
A6	6	1.25	27	40	0.5
B1	18	2	41	40	0.5
B2	6	1.25	27	40	0.5
B3	18	2	61	40	0.5
B4	18	1.25	61	40	0.5
B5	12	1.5	44	50	1
B6	12	1.5	44	50	1
C1	12	1.5	44	50	1
C2	12	1.5	44	50	1
		1.25			
C3	18	1	41	60	1.5
C4	18	2	41	60	1.5
C5	6	2	27	60	1.5
C6	6	1.25	47	60	1.5
D1	18	1.25	61	60	1.5
D2	18	1.25	41	60	0.5
D3	6	2	47	60	0.5
D4	6	2	27	60	0.5
D5	18	1.25	61	60	0.5
D6	6	2	47	60	0.5

Investigating the Elimination Cascade

Utilizing time course pH analysis to initiate the elimination cascade



2-(*p*-tolyl)-4-(trifluoromethyl)-1H-imidazole (100 mg, 442 µmol) was added to a solution of isopropanol/water (7:1, 15 mL) containing NaOH (88 mg, 2.2 mmol) at 23 °C. The pH probe was inserted into the reaction flask and time-course pH measurements were initiated. After 12 minutes, the reaction temperature was increased to 30 °C. The temperature was then increased to 40 °C, 50 °C, and 60 °C after 22, 30, and 38 minutes, respectively. The rate of change of pH was calculated by measuring the initial rate upon temperature adjustment.

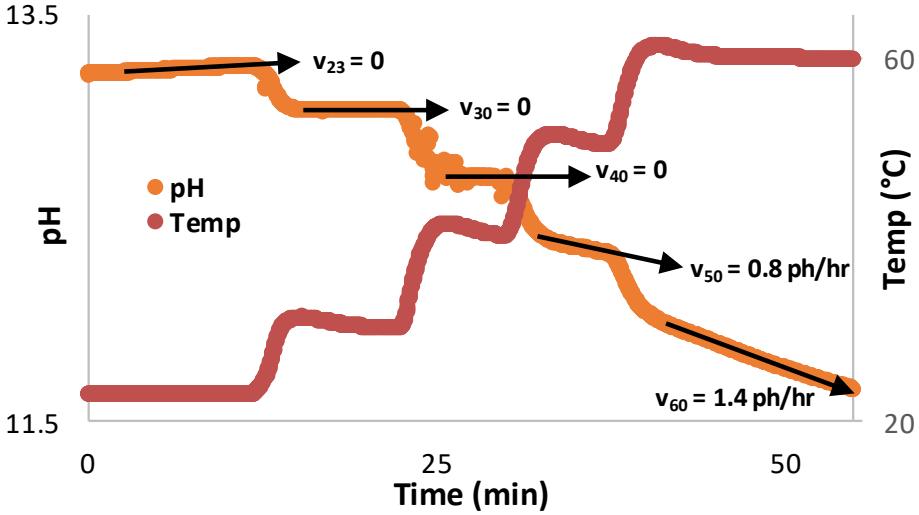


Figure S7: The effects of increasing the reaction temperature on the rate elimination cascade

Measuring the effects of [NH_4OH] on rate and selectivity

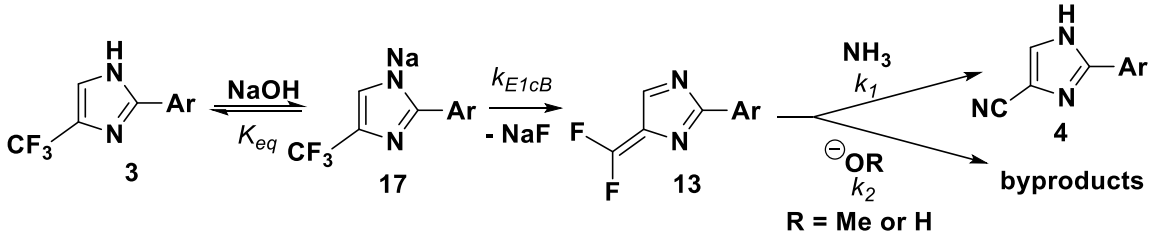


Table S2: Experimental values for Experiments 1-3 to measure the effects of concentration of NH_4OH and reaction rate and selectivity

Expt	Volume NH_4OH	Volume H_2O	Volume MeOH	Volume NaOH
1	0 mL	1.60 mL	8.0 mL	0.44 mL
2	0.80 mL	0.80 mL	8.0 mL	0.44 mL
3	1.60 mL	0.0 mL	8.0 mL	0.44 mL

General Procedure (Expt 2):
2-(*p*-tolyl)-4-(trifluoromethyl)-1H-imidazole (271 mg, 1.20 mmol) was added to a solution of methanol (8.00 mL) and deionized water (0.80 mL). Aqueous (28 wt %) ammonium hydroxide (0.70 g, 0.80 mL, 6.0 mmol) and aqueous (15 M) sodium hydroxide (288 mg, 7.20 mmol) were then added. The reaction temperature was increased to 60 °C and a sampling sequence was initiated. HPLC samples were analyzed using HPLC method 2.

The same general procedure was repeated for both Expts 1 and 3 using the experimental values listed in Table S2.

The same general procedure was repeated for Expt 1 but NaF (50 mg, 1.20 mmol) was added to the reaction before heating to investigate the effects of fluoride on the rate of the reaction (Expt 1 w/ NaF).

HPLC calibration curve data was used to calculate the mole fraction of both **3** and **4** at each time point.

To calculate the concentration and therefore Mole Fraction of the byproducts at each time point the following assumption was made: $[\mathbf{Byproducts}]_t = [\mathbf{3}]_0 - [\mathbf{3}]_t - [\mathbf{4}]_t$

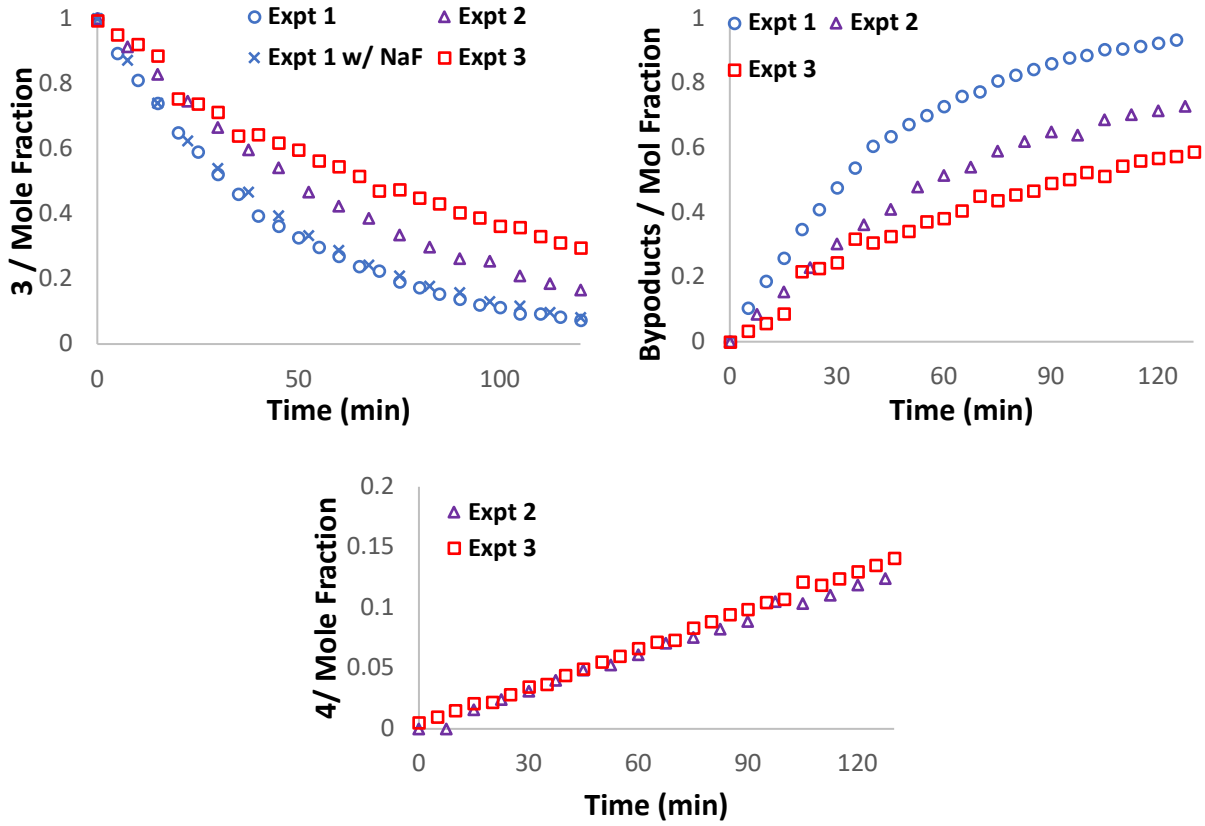
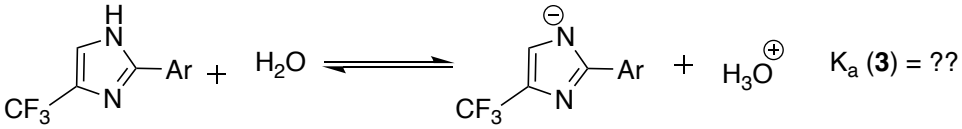


Figure S8: HPLC conversion profiles of **3** for experiments **1** (with and without NaF), 2, and 3 (top left). HPLC formation profiles byproducts for experiments 1, 2, and 3 (top right). HPLC formation profiles of **4** for experiments 2 and 3 (bottom centre).

COPASI model

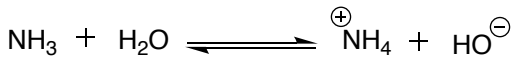
The following model was created in COPASI comprised of the following components

A) Acid – Base reactions: This series of equilibria recapitulates the rapid proton exchange in the reaction and allows the pH to vary dynamically in response to the changing reaction composition.

1) 

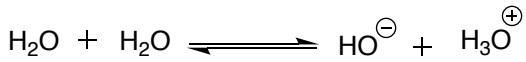
K_a (**3**) = ??

Acid dissociation constant of imidazole – unknown value to be estimated from model

2) 

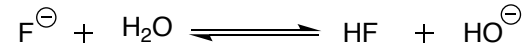
K_b (NH_3) = 1.8 x 10^{-5}

Base dissociation constant for ammonia in water

3) 

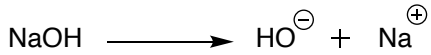
K_w = 1.0 x 10^{-14}

Autoionization of water

4) 

K_b (F^-) = 1.5 x 10^{-11}

Base dissociation constant for fluoride in water

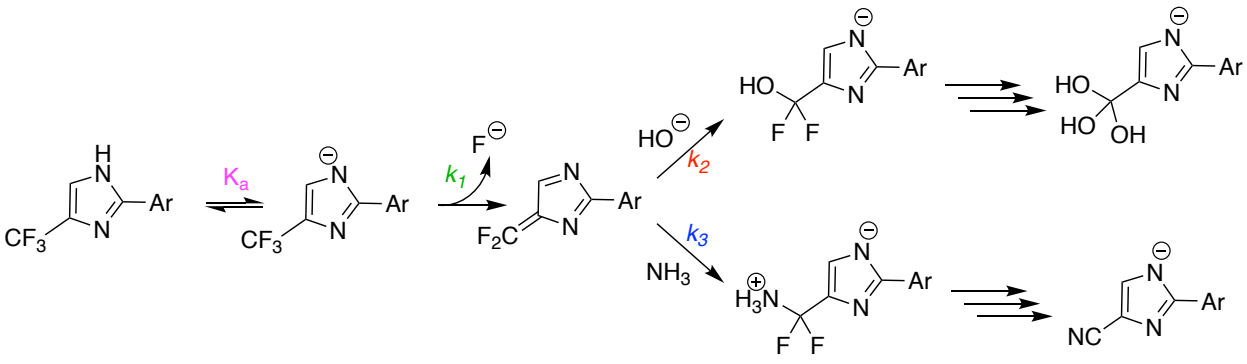
5) 

k_{diss} (NaOH) = 1 x 10^{10}

Dissociation of sodium hydroxide – assumed to be very large and irreversible

B) Reaction pathway

The reaction sequence is assumed to follow the following simplified mechanism.



This sequence assumes that:

a) The initial pre-equilibrium (Ka) to give imidazolate will impact the rate of consumption of imidazole (d[**3**]/dt) and will be impacted by the pH of the solution.
b) Elimination from imidazolate to fulvene represents the first irreversible step in the reaction sequence (k_1). This assumption is supported by the lack of kinetic sensitivity to [F^-].
c) The final product selectivity is determined by competitive capture of the electrophilic fulvene by either oxygen (^-OH) or nitrogen (NH_3) nucleophile. This is approximately given as:

$$\frac{[O]}{[N]} = \frac{k_2[OH^-]}{k_3[NH_3]}$$

d) No cross-over occurs following capture by either oxygen or nitrogen to give intermediates X or Y respectively. Subsequent replacement of F likely proceeds via a sequential elimination-nucleophilic attack cascade, however, the lack of other byproducts suggests that these steps are very rapid for our test case.

This model was applied to the parameter estimation workflow in COPASI, where the time-course concentrations of starting imidazole **3** and products (from oxygen and nitrogen capture) were fit using an evolutionary programming method with a population size of 400 and 200000 generations. The weighting factor for the experimentally determined concentration of starting material was kept low, reflecting the fact that our HPLC method is unable to measure the instantaneous concentration of both imidazole and imidazolate – rather the composite which reports the sum of these two species upon protonation during aliquoting. Input experimental data was obtained from three independent reactions, holding the concentration of imidazole and NaOH constant, allowing only $[NH_4OH]_0$ to be varied. Furthermore, the magnitudes of the literature acid-based equilibria constants (eq 2, 3, 4 and 5) were fixed.

Key results: The model is in excellent agreement with experimental data and recapitulates the changes in rate and selectivity as a function of varied $[NH_4OH]_0$

a) Estimated pKa of imidazole = 9.2, compare to pKa of 2-phenyl-4-(trifluoromethyl)-1H-imidazole = 11[6]
b) Relative selectivity factor for O vs N is 21.6:1 for hydroxide in MeOH.

Individual comparison of experimental (marks) and fitted (line) data are displayed below

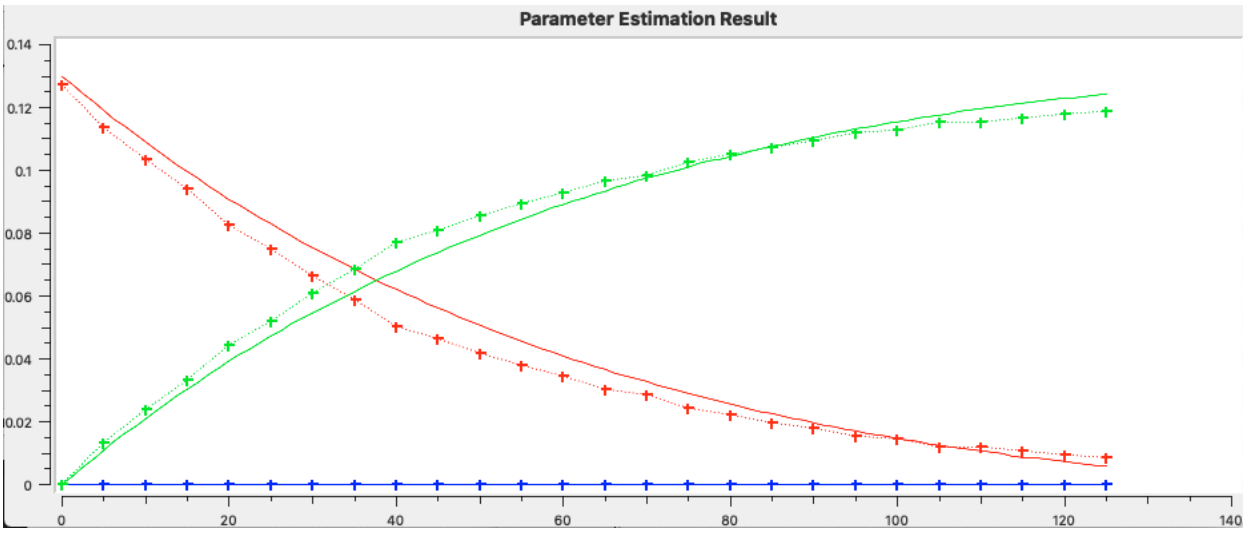


Figure S9: Experiment 1: [imidazole] = 0.13M; [NaOH] = 0.72M; [NH_4OH] = 0M
= [Imidazole]; = [O-Product]; = [CN]

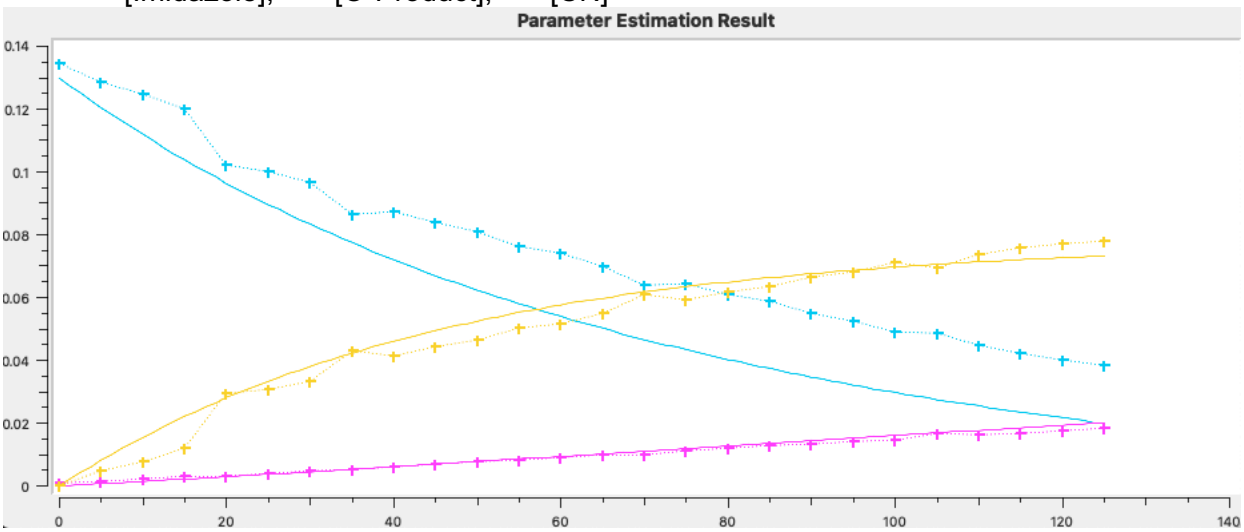


Figure S10: Experiment 2: [imidazole] = 0.13M; [NaOH] = 0.72M; [NH_4OH] = 0.6M
= [Imidazole]; = [O-Product]; = [CN]

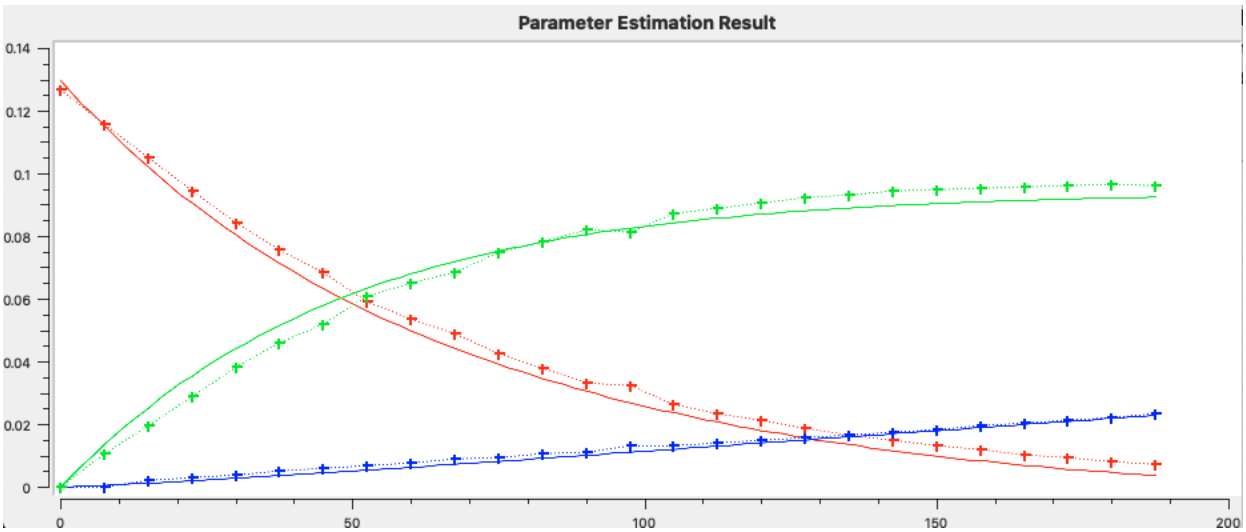


Figure S11: Experiment 3: [imidazole] = 0.13M; [NaOH] = 0.72M; [NH_4OH] = 1.2M
= [Imidazole]; = [O-Product]; = [CN]

Effects of solvent on selectivity

General Procedure:

2-(*p*-tolyl)-4-(trifluoromethyl)-1H-imidazole (271 mg, 1.20 mmol) was added to solvent (8.00 mL), aqueous (28 wt %) ammonium hydroxide (1.6 mL, 12 mmol), and aqueous (15 M) sodium hydroxide (288 mg, 7.20 mmol). The reaction temperature was increased to 60 °C and a sampling sequence was initiated. HPLC samples were analyzed using HPLC method 2.

The general procedure was repeated using isopropanol and methanol as the selected solvents

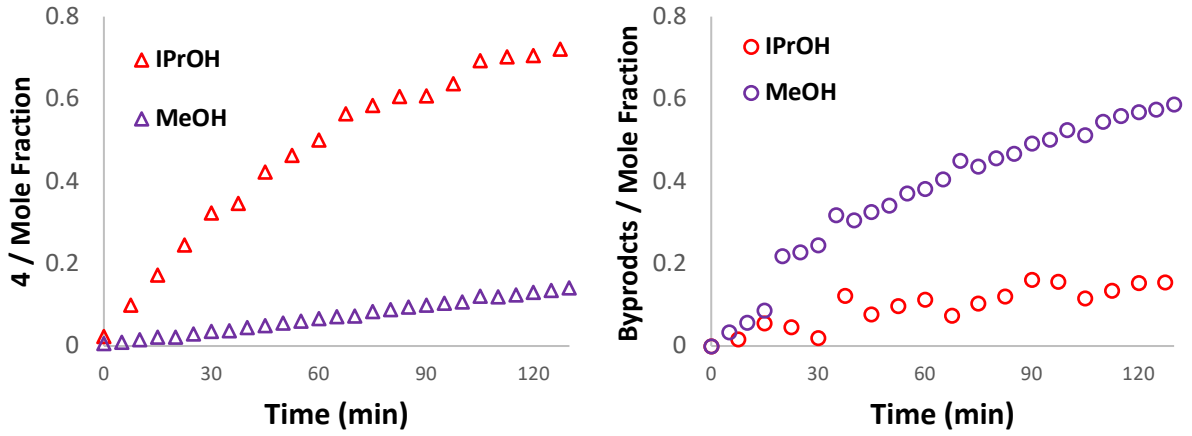
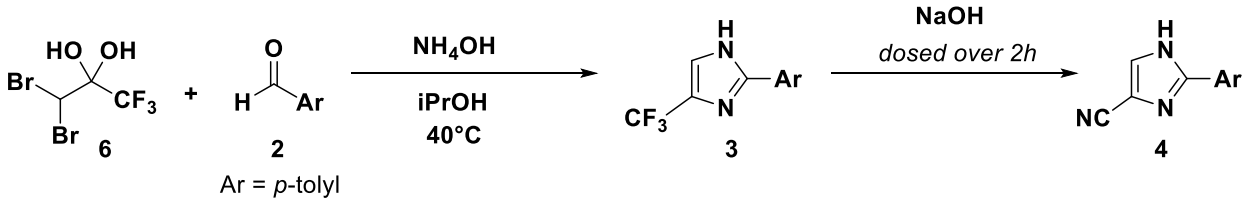


Figure S12: HPLC formation profiles of **4** when either isopropanol (red triangles) or methanol (purple triangles) are selected as the reaction solvents (left). HPLC formation profiles of byproducts when either isopropanol (red circles) or methanol (purple circles) are selected as the reaction solvents (right).

Effects of dosing NaOH on the conversion of 3 to 4



Isopropanol (10.0 mL), aqueous (28 wt %) ammonium hydroxide (6.67 mL, 48 mmol), and 4-methylbenzaldehyde (333 mg, 327 µL, 2.77 mmol) were added to a three necked flask held in an ethylene glycol bath cooled to 0 °C. 3,3-dibromo-1,1,1-trifluoropropan-2-one (1.87 g, 6.9 mmol) was hydrated by adding to water (2.0 mL) cooled in an ice bath over the course of 20 minutes while stirring vigorously to form an aqueous solution of 3,3-dibromo-1,1,1-trifluoropropane-2,2-diol. The aqueous solution of 3,3-dibromo-1,1,1-trifluoropropane-2,2-diol was added to the reaction flask over the course of 20 minutes. Once the addition was complete, the reaction temperature was increased 40 °C (Reaction t_0). A sampling sequence and pH time course measurements were initiated after 225 and 290 minutes of reaction time, respectively. Aqueous (15 M) sodium hydroxide (0.24 g, 3.75 mmol) was added to the reaction after 292, 298, 307, 314, 321, 386, 393, and 412 minutes of reaction time. HPLC samples were analyzed using HPLC method 1.

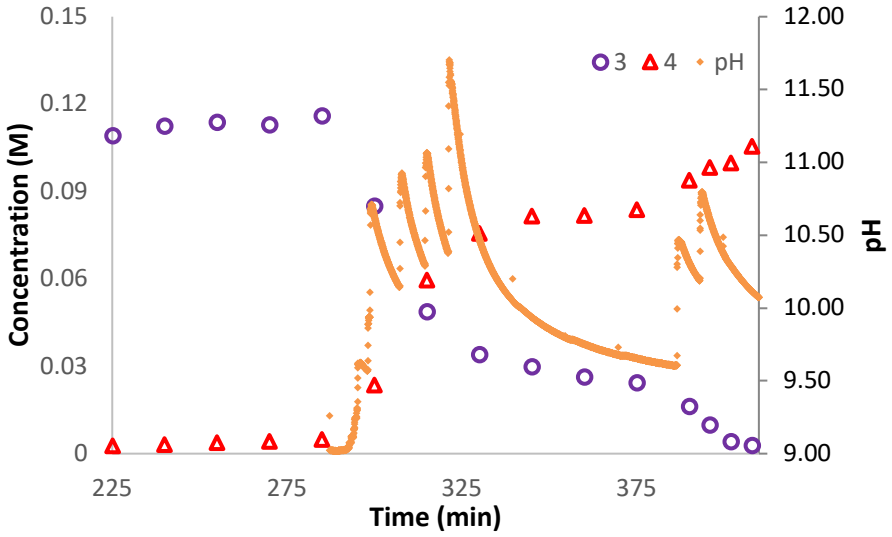
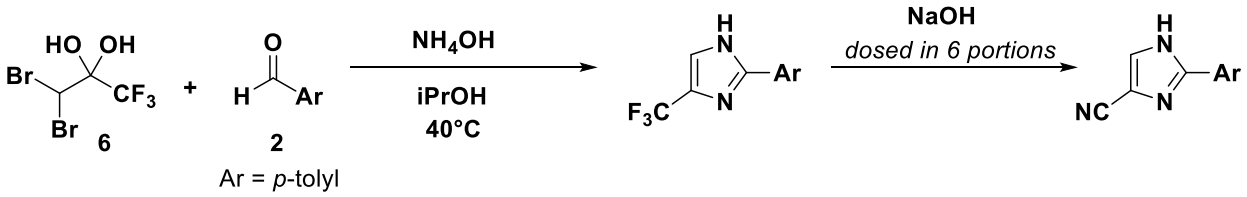


Figure S13: HPLC conversion profile of **3** (red circle) to **4** (purple triangle) while dosing aqueous NaOH. Simultaneous pH time course data are also plotted (orange).

Telescoped Synthesis



Isopropanol (10.0 mL), aqueous (28 wt %) ammonium hydroxide (6.67 mL, 48 mmol), and 4-methylbenzaldehyde (333 mg, 2.77 mmol) were added to a three necked round bottomed flask held in an ethylene glycol bath cooled to 0 °C. 3,3-dibromo-1,1,1-trifluoropropan-2-one (1.50 g, 669 µL, 5.54 mmol) was hydrated by adding to water (1.67 mL) cooled in an ice bath over the course of 20 minutes while stirring vigorously. The aqueous solution of 3,3-dibromo-1,1,1-trifluoropropane-2,2-diol was added to the reaction over the course of 20 minutes. Once the addition was complete, the temperature was linearly ramped from 0 to 60 °C over 180 minutes via iControl and a sampling sequence was initiated. After 300 minutes the pH probe was inserted into the reaction and time course pH measurements were initiated. Aqueous (15 M) sodium hydroxide (110 mg, 2.77 mmol) was added to the reaction via syringe to promote the elimination cascade after 288, 370, 390, 413, 430, and 460 minutes of reaction time. HPLC samples were analyzed using HPLC method 1.

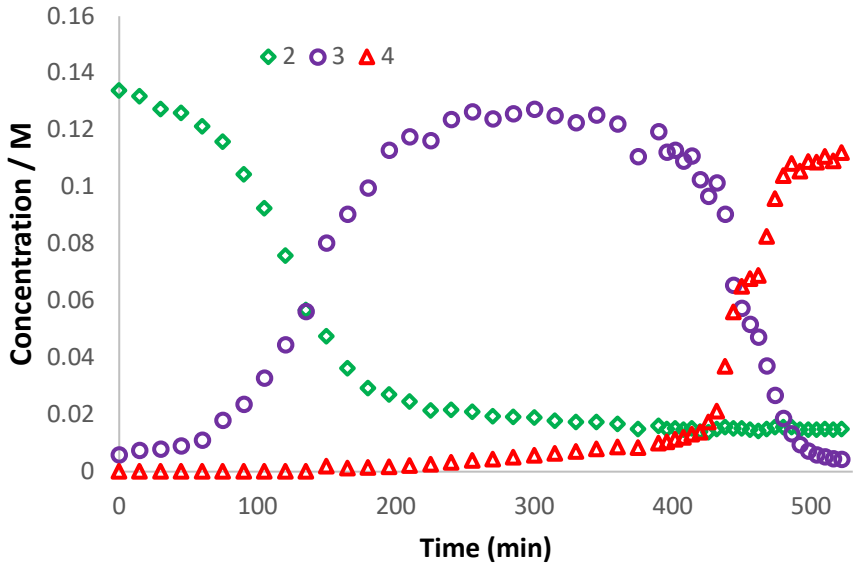


Figure S14: LCMS data for one pot conversion of **2** (green diamonds) into **3** (purple circles) and subsequent conversion of **3** to **4** (red triangles) promoted by dosing NaOH.

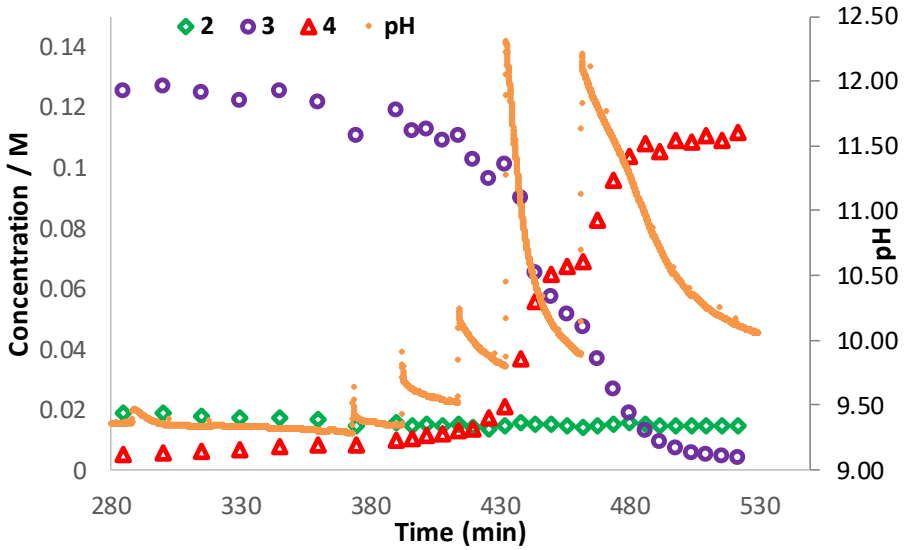


Figure S15: Zoomed in region of the LCMS data for one pot conversion of **2** (green diamonds) into **3** (purple circles) and subsequent conversion of **3** to **4** (red triangles) promoted by dosing NaOH. Simultaneous pH time course data are also plotted (orange).

Scaled up Telescoped Synthesis

To a clean glass 1L jacketed reactor (Vessel 1), 2-propanol (300 mL) and NH_4OH (aq, 28 wt%, 200 mL) were added and cooled to 0 °C. 4-methylbenzaldehye (10 g, 83.23 mmol) was added, maintaining the temperature between 0 to 5 °C. To a clean glass 250 mL jacketed reactor (Vessel 2), water (50 mL) was added and cooled to 0 °C. 3,3-dibromo-1,1,1-trifluoro-propan-2-one (44.92 g, 166.46 mmol, 2 equiv) was added to Vessel 2 over 30 minutes, maintaining a temperature between 0 and 10 °C. The contents of Vessel 2 were then transferred via syringe to Vessel 1 over 30 minutes, maintaining a temperature between 0 and 10 °C. The temperature of Vessel 1 was then linearly ramped from 0 to 60 °C over 180 minutes, and then held at 60 °C for 5 hours. NH_4OH (aq, 28 wt%, 100 mL) was added to Vessel 1, followed by addition of NaOH (aq, 15 M, 33.3 mL, 6 equiv). The NaOH solution was added in 6 equal portions of 5.55 mL, waiting 15 minutes between each addition. After 4.5 hours at 60 °C, additional NH_4OH (aq, 28 wt%, 100 mL) and NaOH (aq, 15 M, 5.55 mL) was added. After 11 h at 60 °C, a third charge of NH_4OH (aq, 28 wt%, 100 mL) was added. After 14 h at 60 °C, the reaction had reached >99% conversion. The contents of Vessel 1 were discharged into a 1L round-bottom flask, and 2-propanol was removed under vacuum (50 mbar). The resulting slurry in water was filtered to give pale orange solids. Cyclopentyl methyl ether (CPME, 100 mL) was added to the solids, and the solution was heated at 100 °C on a hot plate to dissolve the solids. Upon cooling to 20 °C, the resulting slurry was filtered to give off-white solids, which were washed with CPME (10 mL). A second crop was isolated from the filtrate, by addition of hexanes (80 mL) and filtering. The total isolated yield was 89% (16.73 g, 73.96 mmol). The ^{1}H and ^{13}C NMR data match those reported above.

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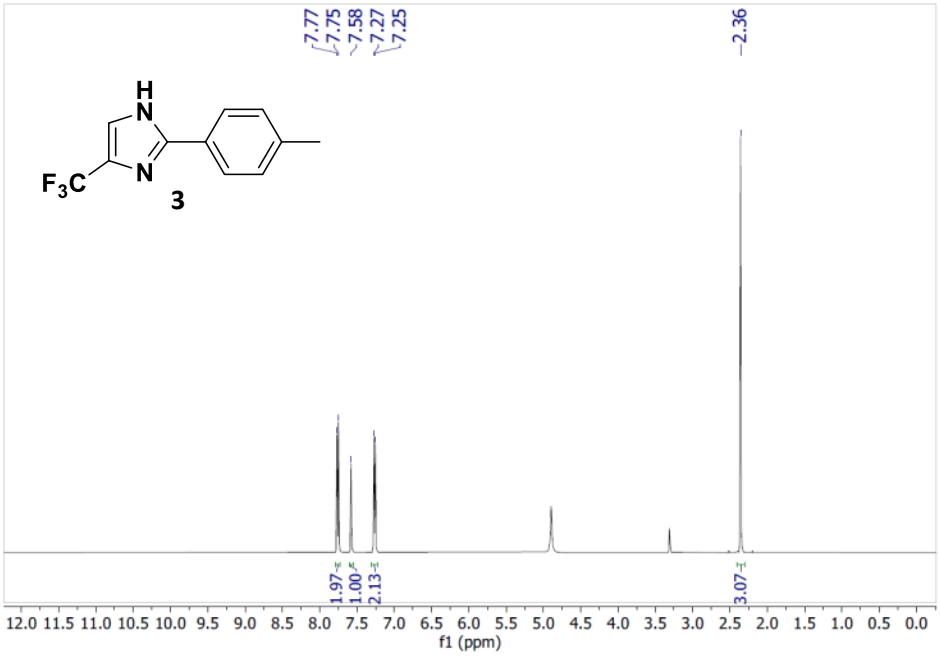
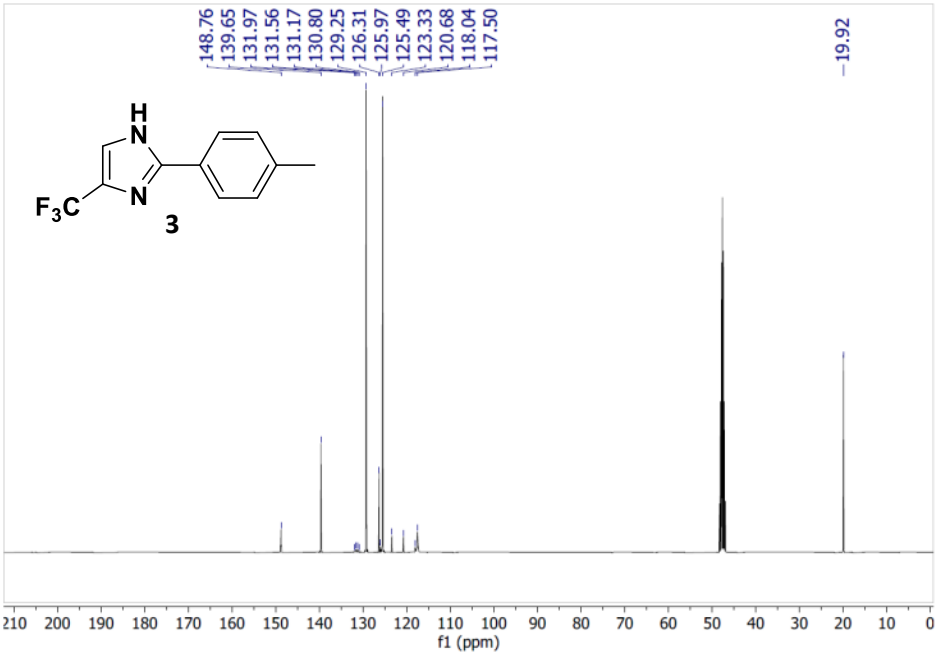
NMR Spectra

2-(*p*-tolyl)-4-(trifluoromethyl)-1H-imidazole (3)

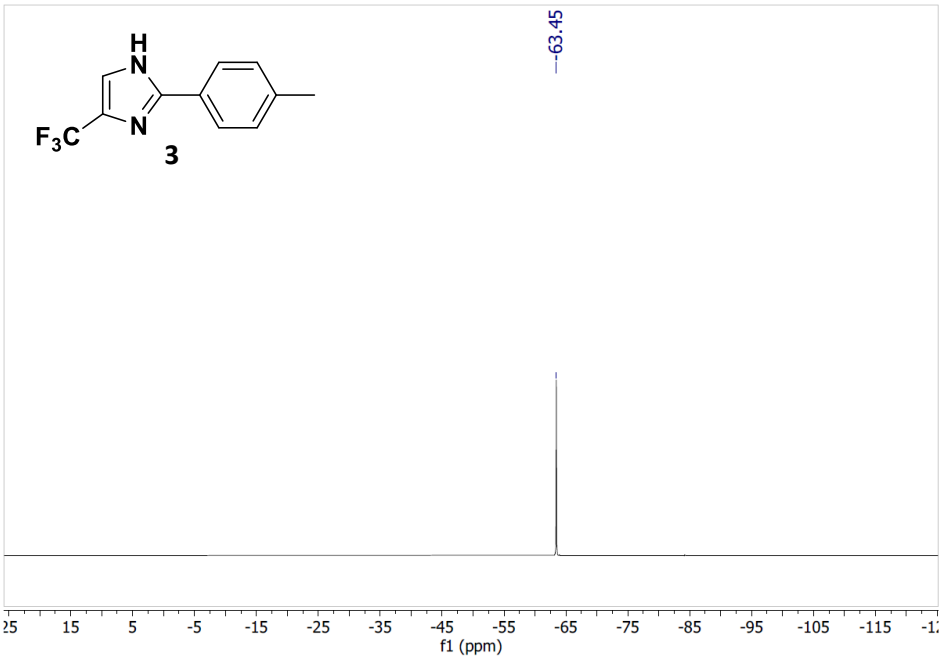
^{1}H NMR in MeOD



^{13}C NMR in MeOD

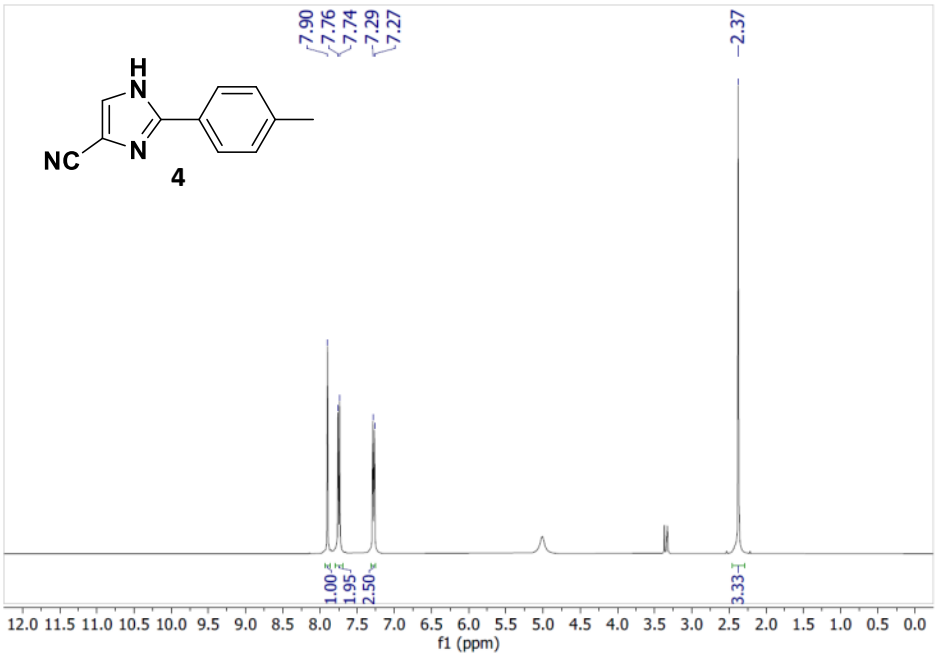


^{19}F NMR in MeOD

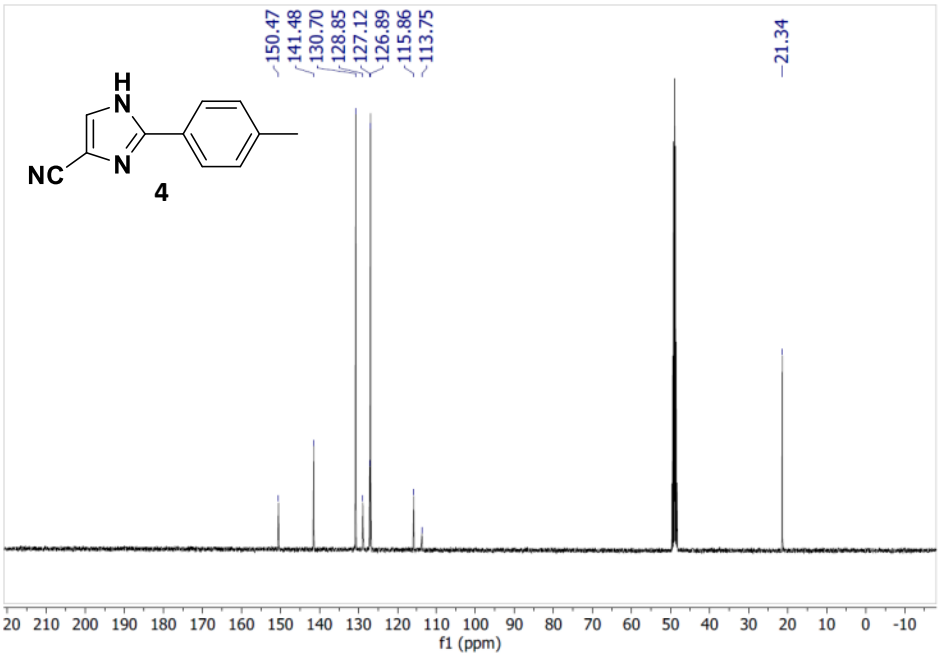


2-(p-tolyl)-1H-imidazole-4-carbonitrile (4):

^{1}H NMR in MeOD

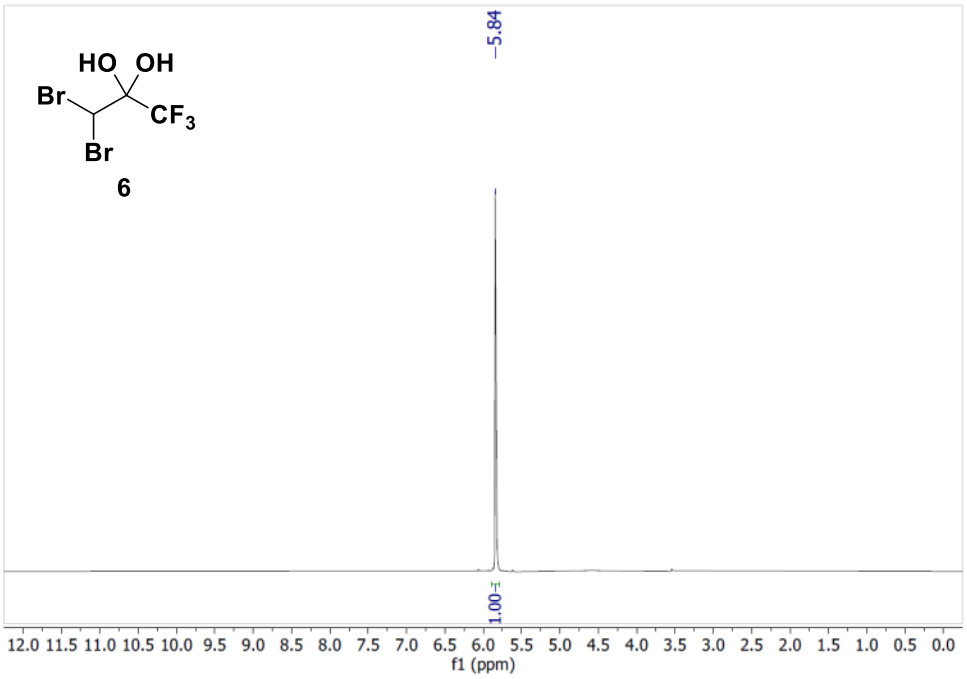


^{13}C NMR in MeOD

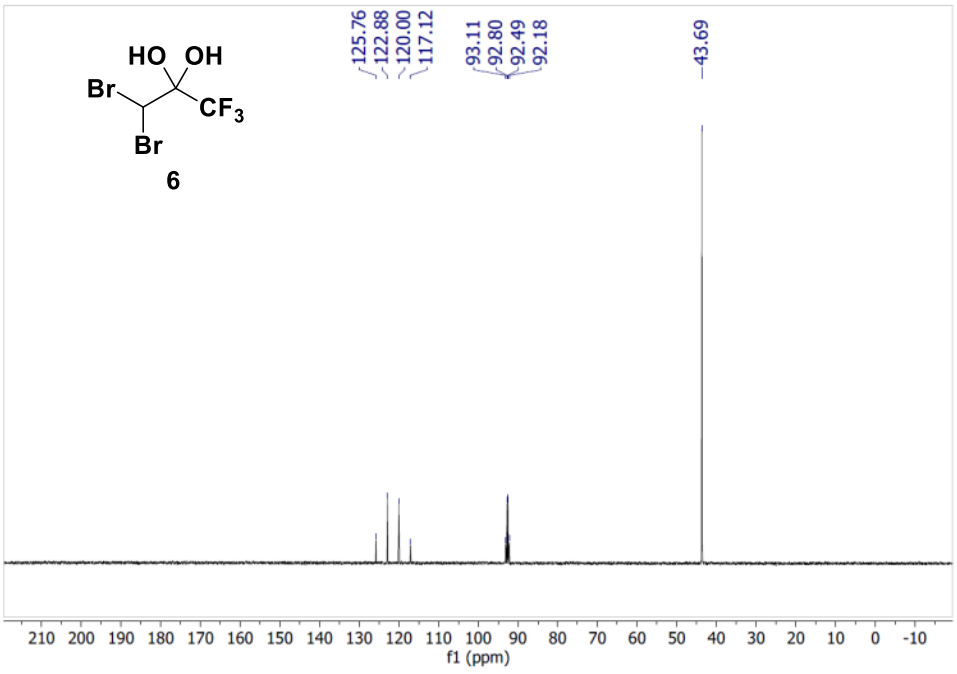


3,3-dibromo-1,1,1-trifluoropropane-2,2-diol (6):

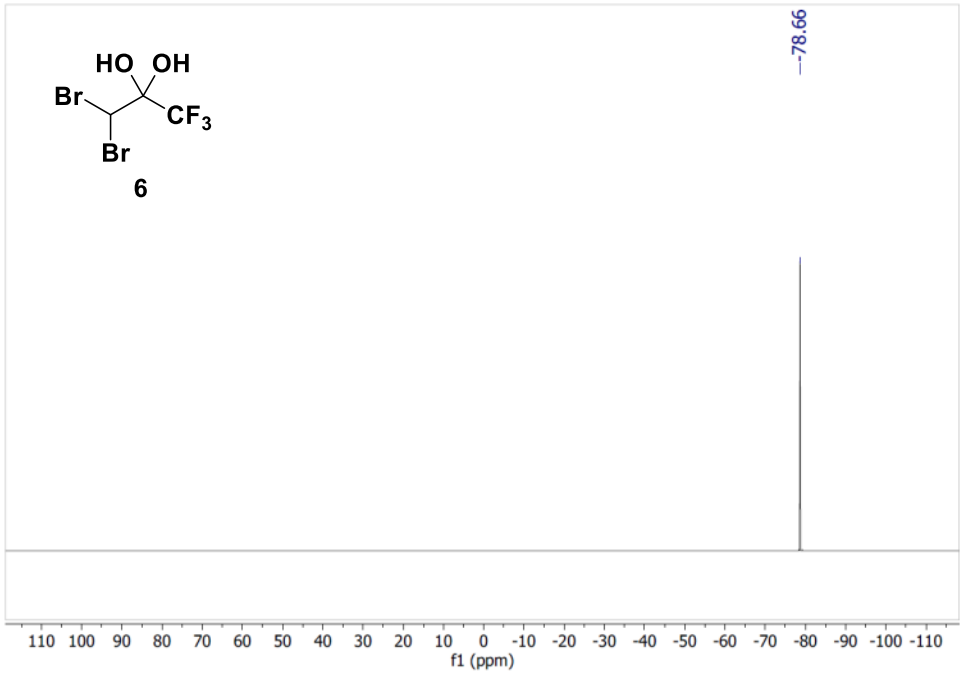
^{1}H NMR in D_2O



^{13}C NMR in D_2O

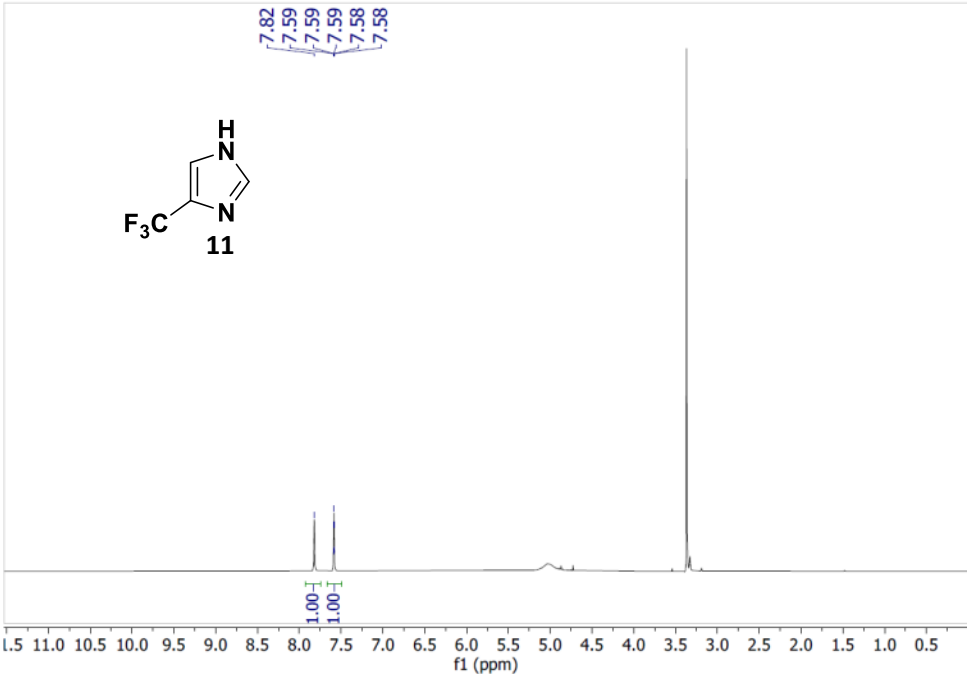


^{19}F NMR in D_2O

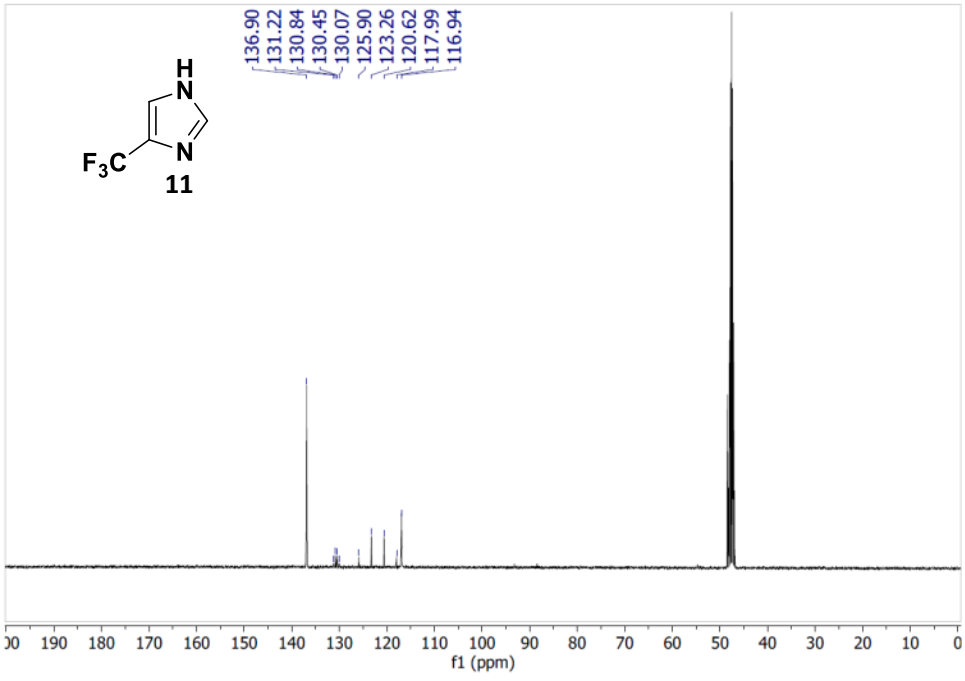


4-(trifluoromethyl)-1H-imidazole (11):

^{1}H NMR in MeOD



^{13}C NMR in MeOD



^{19}F NMR in MeOD