A Practical, Kilogram-Scale Implementation of the Wolff–Kishner Reduction

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Abstract:

A safe and practical strategy has been developed for the large-scale preparation of imidazole 7. The key transformation involved the Wolff–Kishner reduction of the sterically demanding neopentyl-trifluoromethylcyclopropyl imidazole ketone 8. The described process provided the desired product in 74% overall yield without recourse to chromatographic purification. Safety considerations which allowed for the reaction to be conducted safely on kilogram scale are discussed.

Introduction

The deoxygenation of aldehydes and ketones to methyl or methylene derivatives employing hydrazine/KOH first reported by Kishner in 1911[1] and soon thereafter by Wolff in 1912[2] (The Wolff–Kishner reduction) remains one of the most proven, convenient, and synthetically useful processes available for this important type of transformation.[3] The use of higher boiling solvents such as ethylene glycol, diethylene glycol (DEG), and triethylene glycol (TEG) in order to obtain the higher reaction temperatures necessary for successful conversion of carbonyl carbons to methylene derivatives was first introduced by Whitmore[4] and further studied by Soffer.[5] The serendipitously discovered Huang-Minlon modification,[6] which utilizes an excess of safer and less expensive hydrazine hydrate in the presence of alkali, followed by removal of water by distillation subsequent to hydrazone formation, is now the most commonly employed protocol. The generally accepted mechanism involves reversible formation of hydrazone intermediate **2** followed by base-induced proton abstraction to give **4**. Alternatively, hydrazone **2** can react with a second mole of **1** to give azine **3**; however, this process is reversible in the presence of hydra-

Scheme 1
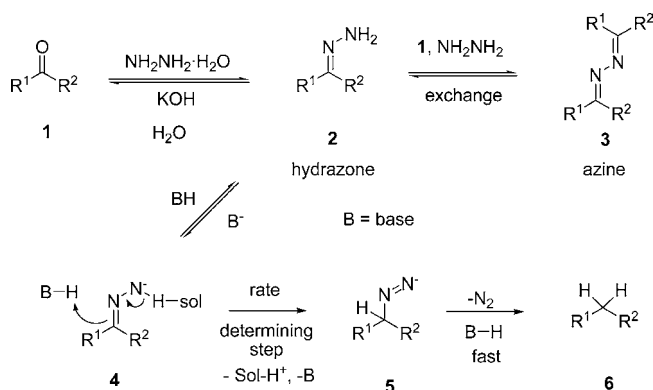
Scheme 2
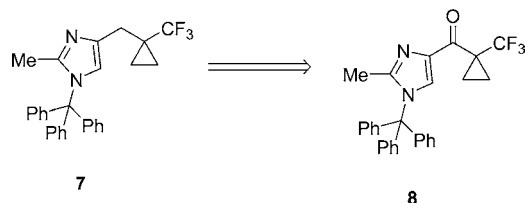
zine.[3b,c] The rate-determining step is transformation of **4** to **5** followed by rapid expulsion of nitrogen and protonation of the resulting carbanion to give the reduced product **6** (see Scheme 1).[3a] It has been reported through mechanistic studies that a minimum temperature of ~190 °C was necessary to achieve reasonable rates of reduction.[7] While the Cram[8] and Henbest[9] modifications allow for the Wolff–Kishner reduction to be carried out at lower temperatures, these methods require the formation and isolation of sensitive hydrazone intermediates of type **2** prior to their reduction. Often irreversible and competitive formation of the corresponding azine **3** has limited the scope and application of these methodologies.

Recently we required kilogram quantities of substituted imidazole **7** in order to support preclinical development of a number of active substrates (Scheme 2). The initial preparation of **7** involved the microwave-mediated Wolff–Kishner reduction of ketone **8** in a sealed vessel at 180 °C and provided **7** in

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Scheme 3

Scheme 4
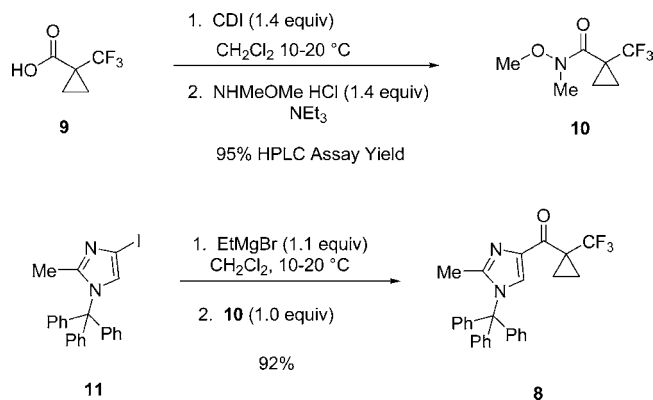
60% yield after chromatography. This procedure presented formidable challenges for scale-up and raised serious concerns regarding safety. Consequently, an alternative protocol for the large-scale synthesis of **7** was required. Key to the successful preparation of **7** would involve conducting the key reduction at lower temperatures, avoiding the use of a sealed tube due to off-gassing, eliminating the use of a microwave, and having a thorough understanding of the reaction in order to safely run it on scale. There have been few reports describing large scale Wolff–Kishner reductions and the issues describing the safe execution of such reactions.[10,11] In this paper we document a practical implementation of a modified Wolff–Kishner reduction of **8** for the kilogram preparation of **7** and outline the key safety concerns that arose from these studies.

Results and Discussion

Our first goal was the development of an efficient synthesis of ketone **8**. Reaction of commercially available 1-trifluoromethylcyclopropane-1-carboxylic acid **9** with 1.4 equiv of 1,1′-carbonyldiimidazole (CDI) in CH$_2$Cl$_2$ was followed by the direct addition of NEt$_3$ and *N,O*-dimethylhydroxylamine hydrochloride and furnished Weinreb amide **10** in 95% HPLC assay yield (Scheme 3). Amide **10** was not isolated, and was used crude in the next step without further purification following an aqueous workup. Treatment of trityl-protected 4-iodoimidazole **11**[12] first with 1.1 equiv of EtMgBr in CH$_2$Cl$_2$ followed by the addition of **10** afforded the desired ketone **8** in 92% isolated yield as a highly crystalline solid.

With the desired ketone **8** in hand our attention turned to the preparation of **7**. The ketone moiety of **8** is flanked by a potentially reactive, sterically demanding neopentyl-trifluoromethylcyclopropyl center and the electron-rich, trityl-protected imidazole core. Reductions which would preserve these sensitive functionalities were particularly attractive. Initial efforts were focused on alternatives to the microwave-mediated Wolff–Kishner reduction employed in the original route. In addition to the
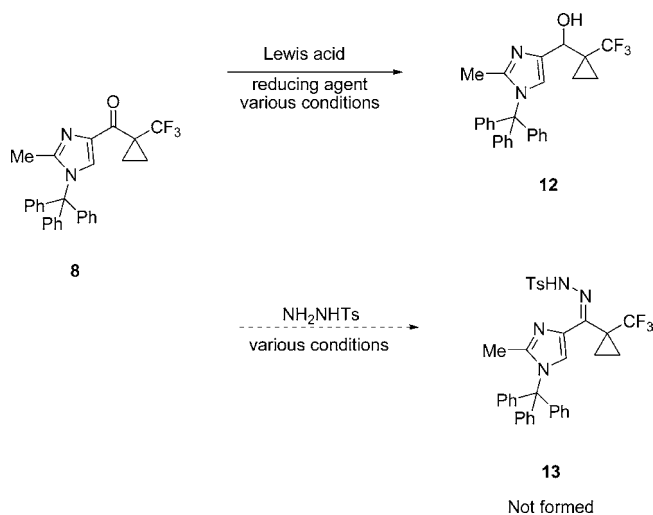
Wolff–Kishner reduction, the direct deoxygenation of ketones to methylene derivatives has been achieved by such methods as Clemmensen reduction,[14] LiAlH$_4$–AlCl$_3$,[15] NaBH$_4$–AlCl$_3$,[16] NaBH$_4$–TFA,[17] borane–BF$_3$,[18] phosphorus–HI,[19] Et$_3$SiH–BF$_3$ or –TFA,[20] Et$_3$SiH–SnCl$_2$,[21] diphenylsilane,[22] triphenylsilane,[23] and catalytic hydrogenation.[24] Due to the potentially reactive trifluoromethylcyclopropyl moiety present in **8**, reductions which proceed through radical-based mechanisms such as Clemmensen and silylhydride-mediated protocols were not considered. Attempted reduction of **8** in the presence of Lewis acids such as AlCl$_3$ and BF$_3$·OEt$_2$ in the presence of a number of reducing agents (LiAlH$_4$, NaBH$_4$, LiBH$_4$, NaCNBH$_3$) only afforded alcohol **12** as the single identifiable product (Scheme 4). No detectable amounts of **7** were observed by either HPLC or NMR of the crude reaction mixtures of these reactions. We speculate that the hindered neopentyl alcohol **12** precluded further reduction to **7** under these reaction conditions. Attempted hydrogenation of **8** was also investigated; however, these reactions were either plagued by over-reduction of the cyclopropyl group, gave exclusively alcohol **12**, or resulted in no reaction.

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Scheme 5
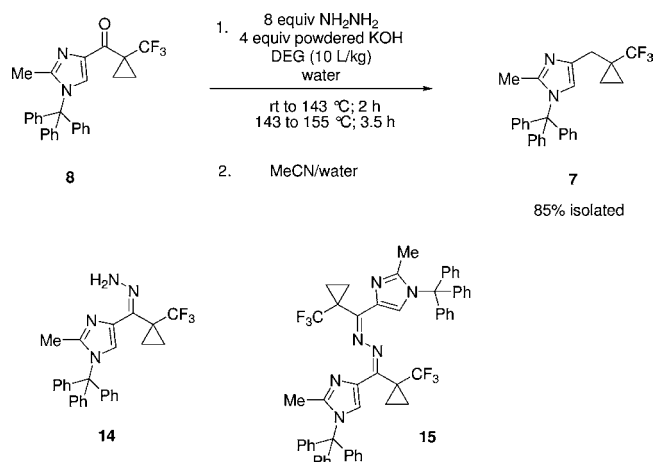
Reduction of tosylhydrazones with borohydride reagents (typically sodium borohydride,[25] sodium cyanoborohydride,[26] catecholborane,[27] or bis(benzoyloxy)borane[28]) or the recently reported reduction of *N-tert*-butyldimethylsilylhydrazones[29] is often employed as an attractive low-temperature alternative for the deoxygenation of ketones. Unfortunately, all attempts to convert **8** into tosylhydrazone **13** were unsuccessful at room temperature and gave significant amounts of decomposition when performed at higher temperatures, and this approach was abandoned.

Having established that alternative methods for the conversion of **8** to **7** were unsuccessful, our attention focused on scale-up of the Wolff–Kishner reduction of **8** (Scheme 5). Preliminary experiments were conducted at 180 °C in diethylene glycol in the presence of 5 equiv of powdered KOH and a large excess of hydrazine hydrate (17 equiv) and furnished **7** in 70% isolated yield after addition of water, extraction of the product, and chromatography of the residue on silica gel. The reaction was then optimized in terms of solvent, temperature, hydrazine hydrate, and KOH charge. After extensive experimentation, it was discovered that the optimal conditions for the conversion of **8** to **7** involved slowly heating a slurry of **8** in diethylene glycol (10 L/kg) in the presence of 8 equiv of hydrazine hydrate (degree of hydration ~1.5, 55% hydrazine), 4 equiv of 85% powdered KOH, and water (~0.23 g/g of hydrazine) to 143 °C (reflux) over 2 h. The addition of water to the reaction mixture minimized the concentration of hydrazine in the head space of the reaction (*vida infra*) and had no detrimental effect on the reaction. The internal reaction temperature was maintained at 143–145 °C for 30 min at which point the HPLC analysis indicated complete consumption of the starting material and formation of a mixture of hydrazone **14**, azine **15**, and product **7**. In order to drive the reaction to completion, the refluxing reaction mixture was diverted to a Dean–Stark apparatus, and the internal temperature was slowly increased to 155 °C over 1 h and was maintained at this temperature for

3–3.5 h. Analysis of the crude reaction mixture by HPLC indicated complete consumption of both **14** and **15**. **Caution: hydrazine is likely to be present and particular care should be taken to avoid contact with any vapors or liquids.** Approximately one-half of the theoretical amount of water in the reaction mixture based on the amount in hydrazine hydrate, KOH, and water added to the reaction mixture was collected in the Dean–Stark trap during the course of the reaction. The majority (~80%) of the water was removed during the initial stages of the distillation between 143 and 155 °C, and distillation completely ceased after 1 h at 155 °C. The safety aspects as well as waste disposal are noted below. The head space temperature above the reaction mixture did not exceed 127 °C at any point during both the heatup and age at 155 °C. The boiling point of hydrazine hydrate is 120 °C, and its flash point is 75 °C. The flammability of aqueous hydrazine decreases, and the flash point increases with increasing dilution with a 40% solution being just ignitable. Due to these considerations, serious concerns regarding the flammability of any vapors in the head space were raised. Therefore, the concentration of hydrazine in the distillate was monitored.[30] The initial distillate collected in the heat up from 143 to 155 °C was found to contain ~1 mg/mL hydrazine. The distillate collected during the 3–3.5 h age was found to contain ~3.9 mg/mL hydrazine, where the combined total distillate was found to be ~2.1 mg/mL hydrazine. These numbers indicated that the majority of hydrazine added to the initial reaction mixture remained in solution with low concentrations in the head space.

Once the reaction was complete, it was cooled to 70–75 °C and the resulting slurry of **7** diluted with MeCN (3 L/kg based on starting material) which helped solubilize unidentifiable polymeric impurities. The reaction mixture was further cooled to 50–55 °C, and water (7 L/kg based on starting material) was added. The reaction mixture was then cooled to rt and filtered. The mother liquors were observed to have a hydrazine concentration of ~16 mg/mL and should be disposed accordingly, see Waste Disposal section below. The wet cake was washed thoroughly with MeCN/water and then with water and dried under vacuum to give **7** in analytically pure form and in 85% isolated yield.

Safety Considerations. Hydrazine is extremely toxic and caution should be taken to avoid prolonged exposure. Hydrazine is rapidly absorbed through the skin and other routes of exposure and appropriate gloves[31] and face shield should be utilized during manipulation. Aqueous hydrazine containing >40 mol% hydrazine is flammable and can support combustion even in the absence of oxygen. While the ignition temperature of hydrazine vapors is 270 °C in the presence of air, a nitrogen atmosphere should be maintained during the heatup, age, and cool-down of the reaction. As long as a ratio of 1.86 mol of water to 1 mol of hydrazine is maintained in the liquid reaction

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(31) Safeskin Purple Nitrile Xtra Exam Gloves, available from Fisher Scientific and impervious to hydrazine, were employed in all operations.

mixture, the vapors in the head space of the reaction cannot become flammable due to the fact that water is more volatile and will be enriched in the vapor phase. Based on the described process, if no more than 325 g of water per kilogram of **7/8** are removed during the distillation of water (raising the temperature to 155 °C), a flammable atmosphere cannot be generated.[32] This was based on the presence of 398 g water/kg **8** from the hydrazine charge, 73 g water/kg of **8** from the KOH water content (~15%), and the addition of 290 g of water/liter hydrazine hydrate charged. In addition, the reaction generates an additional 39 g water/kg of **7** during the course of the reaction. Because this reaction was operating above the flash point (123 °C) of the solvent (diethylene glycol), all ignition sources must be avoided and inertion maintained.

In order to fully evaluate the safety of the Wolff−Kishner reduction of **8**, reaction samples were evaluated by Differential Scanning Calorimetry (DSC)[33,34] and Accelerating Rate Calorimetry (ARC).[35] The starting ketone **8** was found to be thermally unstable (DSC), decomposing with an energy release of 172 Kcal/kg, with a detected onset temperature of 185 °C. The isolated solids and reaction liquors from the end of reaction slurry by DSC were found to be thermally stable below 200 °C. In addition, the isolated product **7** was also found to be thermally stable below 200 °C.

The ARC study was carried out to check for potential exothermic activity in the reaction mixture. The reagents were added to a titanium cell with a stir bar and taken through a series of temperatures to look for heat generation. There was no evidence of hazardous exothermic activity at or below the operating region of the reaction (<160 °C) in the ARC run of the reaction mixture. One mole of gas per mole of substrate (**8**) was observed to form between 80−160 °C. The ARC test did identify a secondary decomposition, generating at least 7 moles of gas per mole of **8**. The onset of this decomposition exotherm was measured at 235 °C,[36] although gas generation was seen earlier, at 180 °C. A more detailed analysis of the decomposition data showed no evidence of autocatalysis. In addition, the temperature at which the adiabatic time to maximum rate was 2 weeks at 183 °C, and the temperature at which the adiabatic time to maximum rate was 24 h at 213 °C. Based on these three facts, it was recommended to control the reaction temperature below 160 °C, with a high temperature alarm to warn of an unexpected temperature increase. To further increase safety, the use of indirect heating, such as Syltherm jackets, is preferred. This both enables better avoidance of overshoot during the heat-up of the reaction mixture and allows the jacket to provide a means of cooling if the temperature rises unexpectedly. The use of this type of reaction vessel, while preferred, is not absolutely required as long as a slow, controlled heatup from 145 to 155 °C is maintained.

Due to the potential interaction of hydrazine with metal and metal oxides, only glass and/or Teflon surfaces should be in contact with the hot reaction mixture. If a stainless steel vessel is to be employed, it should be carefully checked for rust or corrosion prior to use. The high reaction temperatures in conjunction with KOH also results in slight etching of glass vessels.[37]

Waste Disposal. Hydrazine is rapidly destroyed by commercial bleach (5%), and aqueous waste streams may be processed with alkali and bleach prior to disposal.[38,39] Alternatively, hydrazine is neutralized with hydrogen peroxide.[39] According to the International Register of Potentially Toxic Chemicals (IRPTC), hydrazine can be diluted with water and neutralized with dilute sulfuric acid prior to disposal. Hydrazine waste can be diluted with alcohol or another hydrocarbon and burnt in a chemical incinerator equipped with an after-burner and effectively scrubbed. It is advised that adequate commercial bleach be on hand to rapidly destroy any spilled material.[40]

Conclusion

In conclusion, we have demonstrated a safe and practical method for the kilogram preparation of the highly functionalized imidazole **7** which involved the Wolff−Kishner reduction of ketone **8**. The three step sequence provided **7** in 74% overall from acid **9** and required no chromatographic purifications. Key to the successful implementation of this reaction was a thorough understanding of the safety margins within which the reaction could be conducted. This included temperature, amount of water removed from the reaction, and amount of water remaining in the reaction mixture which ensured no flammable atmosphere would be encountered. While this reaction was safely and efficiently conducted on kilogram scale, further scale-up of this reaction, or any Wolff−Kishner reduction, would require further testing of all the reaction parameters prior to execution.

Experimental Section

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate−hexane mixture as the eluent. The water content (KF) was determined by Karl Fisher titration. Hydrazine concentrations were monitored as follows: hydrazine was eluted at room temperature from an Ion Pac CS 17 (4 × 250 mm) with 6 mM methane sulfonic acid using an electochemical detector, injection volume of 100 μL, flow rate 1.0 mL/min.[30] Post column, 0.1 N NaOH was mixed with the stream for electrochemical detection. Standards of hyrazine and unknowns were freshly prepared for quantitation (9:1 water/MeOH). Retention time of hydrazine was 3.1 min.

Preparation of 1-Trifluoromethyl-cyclopropanecarboxylic acid methoxy-methyl amide (10). In a 75 L round-bottom flask[37] charged with 40.0 L of CH_2Cl_2 was added 4.00 kg (26.0

(32) A flammable atmosphere would be one containing >38 mol % hydrazine.
(33) The DSC runs were conducted on TA Instruments 2920 DSC cells operating under TA Instruments' Thermal Advantage software, ver. 1.1 A. A reusable pressure-tight cell made of either Hastelloy B-2 or tantalum-lined Hastelloy B-2 was used.
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(36) An onset threshold of 0.025 K/min was used, and the adiabatic correction (φ) factor was 1.27.
(37) A glass vessel was employed. Etching was significant after three consecutive runs in the same flask.
(38) Armour, M. A. *Hazardous Laboratory Chemicals Disposal Guide*; CRC Press: Boca Raton, FL, 1991; pp 170−171.
(39) Speer, S. E.; Pasricha, A.; Quinn, R. F. *Ind. Water Treatment* **1995**, 48.
(40) For an alternative waste disposal procedure, see ref 10.

mol) of 1-(trifluoromethyl)cyclopropane-1-carboxylic acid **9** at rt. The solution was cooled to 10 °C, and 5.89 kg (34.3 mol) of 1,1′carbonyldiimidazole (CDI) was added in portions over 1 h, maintaining the reaction temperature below 20 °C. The addition of CDI was slightly exothermic, and CO_2 gas was evolved. The reaction was stirred at rt for 30 min, and 5.07 L (36.3 mol) of NEt_3 was added in one portion followed by 3.54 kg (36.3 mol) of *N,O*-dimethylhydroxylamine hydrochloride. The resulting mixture was stirred at rt for 15 h and then reverse quenched into a cooled (5 °C) 3 N HCl solution (25.0 L). The layers were separated, and the organic layer was washed sequentially with 25 L of saturated aqueous $NaHCO_3$ and 25 L of water. The organic layer was passed through a plug of anhydrous Na_2SO_4 (KF < 1000 ppm) and then concentrated under vacuum to give 4.86 kg (95%) of **10** which was sufficiently pure for use without further purification. An analytical sample was prepared by passing over a plug of silica gel to give **10** as a colorless liquid: ^{1}H NMR (CDCl₃, 400 MHz) δ 1.24 (m, 2H), 1.27 (m, 2H), 3.26 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (CDCl₃, 100 MHz) δ 9.9, 28.0 (q, $J = 31.0$ Hz), 34.1, 53.4, 60.9, 124.1 (q, $J = 271.0$ Hz), 165.0; ^{19}F NMR (CDCl₃, 75 MHz) δ −66.7.

Preparation of (2-Methyl-1-trityl-1H-imidazol-4-yl)-(1-trifluoromethyl-cyclopropyl)-methanone (8). Into a 75 L round-bottom flask charged with 35.0 L of CH_2Cl_2 was added 5.93 kg (13.2 mol) of **11**[12] at rt. The solution was cooled to 5 °C, and 4.40 L (13.2 mol) of EtMgBr (3.0 M in Et₂O) was added while maintaining the internal reaction temperature below 25 °C. The reaction was stirred at rt for 5 min postaddition of the EtMgBr. To the solution was added in one portion 2.36 kg (12.0 mol) of **10** in 5 L of CH_2Cl_2. The resulting mixture was stirred at rt for 15 h and then reverse quenched into a solution of 40 L of 5% KH_2PO_4. The layers were separated, and the organic layer was washed with 40 L of saturated aqueous $NaHCO_3$. The organic layer was concentrated under reduced pressure 15−25 °C to remove about 20 L of the solvent. Isopropanol (25 L) was slowly added while concentration was continued to a final volume of approximately 25 L. The resulting slurry was heated to 60 °C for 1 h, and 25 L of water was added over 1 h. The slurry was aged at 60 °C for 1 h, cooled to rt, and filtered. The wet cake was washed with 12 L of 1:2 isopropanol/water and dried under vacuum/N_2 sweep to afford 5.24 kg (97.7 wt %, 92%) of **8** as a colorless solid: mp 134−135 °C; ^{1}H NMR (CDCl₃, 400 MHz) δ 1.44 (m, 2H), 1.62 (s, 3H), 2.25 (m, 2H), 7.12 (m, 6H), 7.14 (s, 1H), 7.35 (m, 9H); ^{13}C NMR (CDCl₃, 100 MHz) δ 13.1, 17.4, 27.4, 33.6 (q, $J = 30.0$ Hz), 75.9, 123.9 (q, $J = 271.0$ Hz), 128.3, 129.3, 129.9, 130.1, 136.7, 141.4, 147.6, 188.1; ^{19}F NMR (CDCl₃, 75 MHz) δ −68.0. Anal. Calcd For $C_{28}H_{23}F_3N_2O$: C, 73.03; H, 5.03; N, 6.08. Found: C, 72.89; H, 4.99; N, 6.01.

Preparation of 2-Methyl-4-(1-trifluoromethyl-cyclopropylmethyl)-1-trityl-1H-imidazole (7). In a 72-L round-bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condensor was charged 2.49 kg (5.28 mol, 97.7 wt %) of **8** as a solid and 1.18 kg (21.1 mol) of powdered KOH (∼85%, charge not based on wt % of KOH). To the flask was then charged sequentially 25 L of diethylene glycol, 2.10 L of hydrazine hydrate, and 500 mL of water. The stirring was started, and the reaction mixture was heated to an internal temperature of 143 °C over a 2-h period at which point the reaction mixture was refluxing. The reaction was maintained at this temp for ∼30 min, and the refluxing mixture was diverted to an inline Dean−Stark apparatus, and water began to collect in the apparatus. **Caution: hydrazine is likely to be present and particular care should be taken to avoid contact with any vapors or liquids.** After approximately 300 mL of water had collected, the internal reaction temperature was increased to 155 °C over a 45 min period, and the reaction mixture stirred at this temperature for 3−3.5 h during which time a total amount of ∼790 mL of water had collected. The reaction mixture was then allowed to cool to ∼ 70−75 °C, and the sides of the flask were rinsed with 7.5 L of MeCN into the reaction mixture. The resulting slurry was further cooled to ∼55 °C, and 17.5 L of water was added dropwise. The slurry was allowed to slowly cool to rt and stirred overnight at rt. The slurry was filtered[41] and the wet cake was washed with 35 L of 1:1.5 MeCN:water and then with 25 L of water and dried under vacuum/N_2 sweep to give 2.00 kg (85%) of **7** as an analytically pure white solid: mp 165−166 °C; ^{1}H NMR (CDCl₃, 400 MHz) δ 0.70 (m, 2H), 0.84 (m, 2H), 1.61 (s, 3H), 2.93 (s, 2H), 6.49 (s, 1H), 7.12 (m, 6H), 7.32 (m, 9H); ^{13}C NMR (CDCl₃, 100 MHz) δ 7.0, 17.3, 22.1 (q, $J = 31$ Hz), 27.5, 74.8, 119.9, 124.1 (q, $J = 271.0$ Hz), 126.4, 127.8, 128.1, 133.3, 142.5, 146.5; ^{19}F NMR (CDCl₃, 75 MHz) δ −71.4. Anal. Calcd For $C_{28}H_{25}F_3N_2$: C, 75.32; H, 5.64; N, 6.27. Found: C, 75.42; H, 5.66; N, 6.23.

Characterization of (2-methyl-1-trityl-1H-imidazol-4-yl)-(1-trifluoromethyl-cyclopropyl)-methanol (12): Colorless oil: ^{1}H NMR (CDCl₃, 400 MHz) δ 0.72 (m, 1H), 0.85 (m, 2H), 0.91 (m, 1H), 1.62 (s, 3H), 4.07 (br s, 1H), 5.08 (s, 1H), 6.32 (s, 1H), 7.12 (m, 6H), 7.32 (m, 9H); ^{13}C NMR (CDCl₃, 100 MHz) δ 5.3, 7.4, 17.2, 27.8 (q, $J = 31$ Hz), 66.0, 75.1, 118.2, 128.0, 128.3 (q, $J = 271.0$ Hz), 128.4, 130.0, 137.7, 142.3, 146.7; ^{19}F NMR (CDCl₃, 75 MHz) δ −67.9.

(41) The filtrate containing aqueous hydrazine waste was disposed of by careful dilution with commercial bleach and sent for disposal to an outside vendor.