

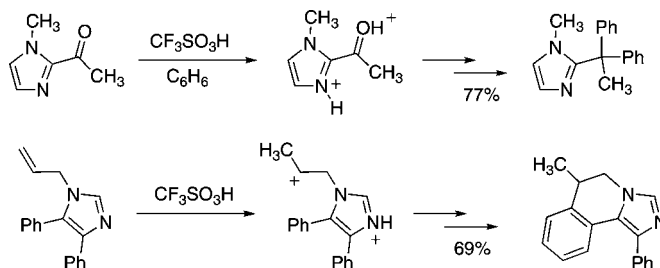
Superelectrophilic Chemistry of Imidazoles

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Received December 23, 2008



The mechanistic and synthetic chemistry of imidazole-based superelectrophiles has been studied. The protonated imidazole ring, or imidazolium group, is shown to enhance the electrophilic reactivity of an adjacent carboxonium group (compared to a related monocationic species). This leads to efficient condensation reactions between imidazole aldehydes and ketone with arenes in the Brønsted superacid $\text{CF}_3\text{SO}_3\text{H}$. The imidazole-based superelectrophiles are shown to be useful in other reactions leading to functionalized heterocycles. The imidazolium group may also trigger charge migration reactions in dicationic species.

Introduction

The concept of superelectrophilic activation was first proposed by Olah and co-workers in the 1970s.¹ Since these pioneering studies, there have been many example of superelectrophiles described in the literature.² As a consequence of their high reactivities, superelectrophiles can be used in synthetic transformations with very weak nucleophiles, including alkanes and deactivated arenes. A number of studies have shown that *N*-heterocyclic systems may also be a part of superelectrophilic systems.³ These superelectrophilic reactions have been used to prepare a variety of functionalized *N*-heterocyclic products.

Imidazoles are well-known for their diverse biological activities and consequently are a privileged class of compounds among pharmaceutical substances.⁴ Little work has been done to determine the scope of superelectrophilic imidazole chem-

istry.⁵ As reactive intermediates, it is expected that superelectrophiles can be the basis for new synthetic methods leading to functionalized imidazoles. In this Article we describe the chemistry of superelectrophiles having the imidazole ring system. We demonstrate that the imidazolium cation may significantly activate adjacent electrophilic sites. This superelectrophilic activation represents a useful structure–reactivity

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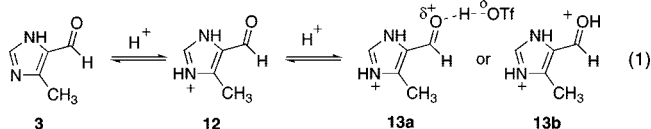
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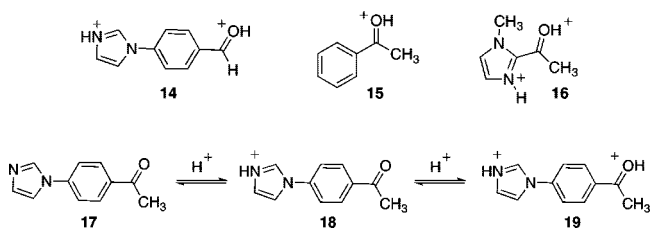
relationship with imidazole-based electrophiles. It is used to prepare novel products by synthetic reactions on the imidazole side chains.

Results and Discussion

The hydroxyalkylation reaction involves the acid-catalyzed condensations of aldehydes and ketones with aromatic compounds.⁶ It is used industrially to prepare polymers, fine chemicals, and pharmaceutical substances. Recently, several hydroxyalkylation reactions have been reported involving *N*-heterocycle-based superelectrophiles (pyridines, thiazoles, and quinolines).^{3a,b} We have found that imidazole-based superelectrophiles are also very efficient reactants in the hydroxyalkylation reaction (Table 1). Similar diarylalkylimidazoles have shown activity as aromatase inhibitors,⁷ and this condensation chemistry involves a simple and improved route to these products. A mechanism is proposed in which the acid initially protonates the imidazole ring and an equilibrium is established with the diprotonated superelectrophile (eq 1). The involvement of the superelectrophile **13a,b** is consistent with need for strong and superacidic media for good conversions (entry 3).



Superelectrophile **13** is capable of reacting with moderately deactivated arenes, such as 1,3-dichlorobenzene (entry 4). In contrast, benzaldehyde does not react with 1,3-dichlorobenzene in $\text{CF}_3\text{SO}_3\text{H}$ under similar reaction conditions, demonstrating that the imidazolium cation activates the adjacent carboxonium ion in dication **13**. When compound **4** is reacted with $\text{CF}_3\text{SO}_3\text{H}$ and C_6H_6 , the condensation product is formed in good yield, suggesting that the imidazolium ion is capable of activating the carboxonium ion despite being separated by the phenyl group (**14**). The acetyl-substituted imidazole (**5**) also condenses with benzene in $\text{CF}_3\text{SO}_3\text{H}$ (entry 6). This observation is notable because a similar condensation reaction cannot be done with acetophenone. In triflic acid, acetophenone is almost completely protonated;⁸ however, cation **15** is not sufficiently electrophilic to react with benzene. The imidazole system **5** forms a carboxonium ion (**16**) with an adjacent imidazolium cation, leading to the observed superelectrophilic reactivity. When 1-(4-(1*H*-imidazol-1-yl)phenyl)acetophenone (**17**) is reacted with triflic acid and benzene, no condensation reaction is observed. In contrast to dication **14**, the distant imidazolium ion in dication **19** does not sufficiently activate the carboxonium ion for reaction with benzene.



In addition to the above condensation reactions, imidazole-based superelectrophiles may possess very reactive carbocationic centers. Previously, we have described Friedel–Crafts-type

TABLE 1. Hydroxyalkylation Reactions of Imidazole Derivatives 1–5 with Acid and Arene^a

entry	substrate	product	yield (acid)
(1)			93% ($\text{CF}_3\text{SO}_3\text{H}$)
(2)			99% ($\text{CF}_3\text{SO}_3\text{H}$)
(3)			99% ($\text{CF}_3\text{SO}_3\text{H}$) 15% (H_2SO_4) 0% ($\text{CF}_3\text{CO}_2\text{H}$) ($\text{CH}_3\text{SO}_3\text{H}$) (H_3PO_4)
(4)			21% ($\text{CF}_3\text{SO}_3\text{H}$)
(5)			98% ($\text{CF}_3\text{SO}_3\text{H}$)
(6)			77% ($\text{CF}_3\text{SO}_3\text{H}$)

^a For entries 1–3, 5, and 6 reaction was with benzene; for entry 4 reaction was with 1,3-dichlorobenzene.

reactions involving olefinic imidazoles, including intra- and intermolecular reactions.^{3a,5a} As extensions of these methodologies, we have found that intramolecular reactions are capable of producing the *H*-imidazo[5,1-*a*]isoquinoline type of ring system. For example, 4,5-diphenylimidazole reacts with styrene oxide to give the benzylic alcohol (**20**), which upon ionization in superacid gives the cyclization product **23** (eq 2). The conversion involves formation of the superelectrophilic dication **21**, cyclization to **22**, *ipso*-protonation of the phenyl group on **22**, and benzene elimination to give product **23**. In an attempt to prepare the imidazo[2,1-*a*]isoquinoline ring system (**26**), alcohol **24** was ionized in superacid (eq 3). The cyclized product **25** is formed in good yield at 25 °C; however, little or no imidazo[2,1-*a*]isoquinoline (**26**) is produced. At higher temperatures, the reaction of **24** in $\text{CF}_3\text{SO}_3\text{H}$ leads to a complex mixture of decomposition products. With the allyl-substituted imidazoles (**27** and **30**), reaction in superacid leads to efficient formation of the dicationic superelectrophiles (**28** and **31**), and the cyclization products (**29** and **32**) are formed in reasonably good yield (eqs 4 and 5). Besides generating superelectrophilic carbocationic centers from olefins and alcohols, the ether group

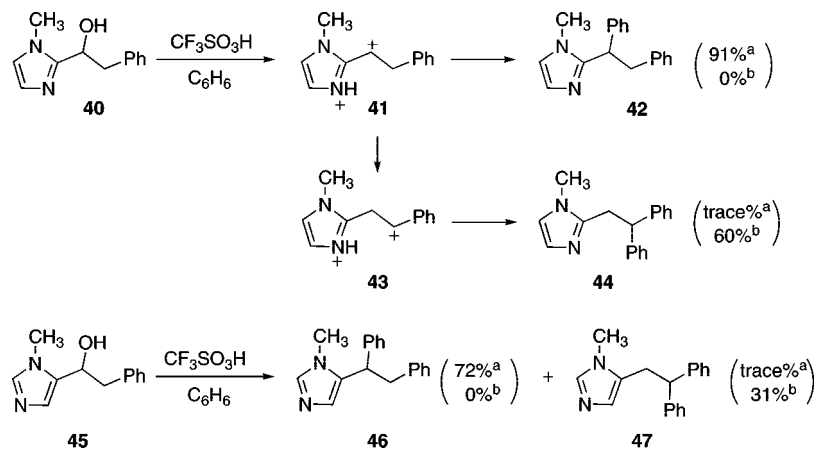
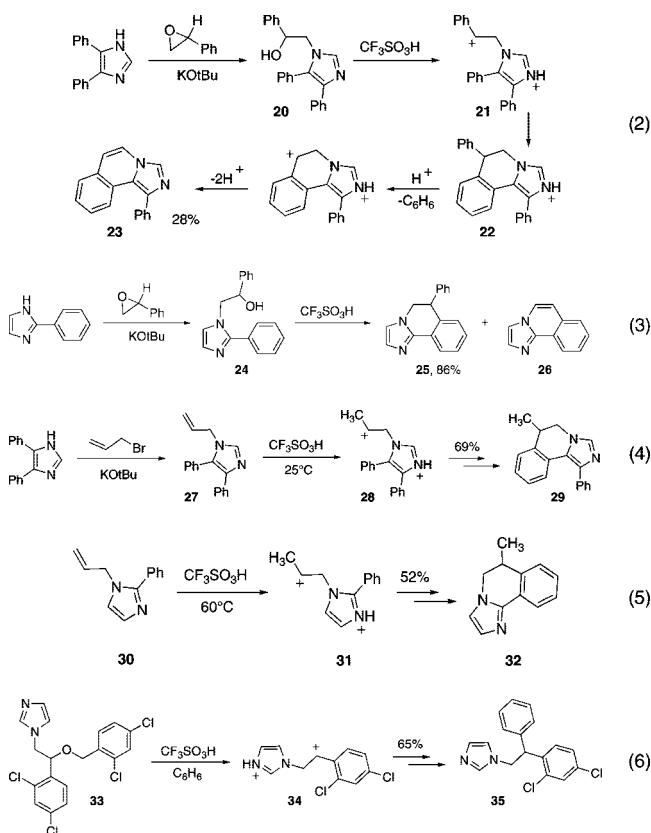


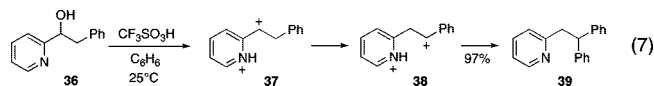
FIGURE 1. Charge migration experiments with imidazoles **40** and **45**.

of the antifungal drug miconazole (**33**) reacts in superacid to give the dicationic species (**34**, eq 6). In the presence of benzene, superelectrophile **34** further reacts to give the Friedel–Crafts product **35**.



We have also studied imidazole-carbocations and their tendency to undergo charge migration reactions. Recently, our group described the charge migration reactions of various dicationic *N*-heterocyclic systems, such as in the pyridine derivative **36** (eq 7).⁹ The charge migration converts an initial 1,3-dication (**37**) to the 1,4-dication (**38**), a transformation driven largely by charge–charge repulsive effects. Two imidazole-based systems were examined in the present study and showed some tendency for charge migration (Figure 1). The imidazole substrates (**40** and **45**) were prepared from reactions of the aldehydes using benzylmagnesium chloride.¹⁰ Reaction of the Grignard reagent with 1-methyl-1*H*-imidazole-2-carboxal-

dehyde directly provided compound **40**, whereas a similar reaction with 1-methyl-1*H*-imidazole-5-carboxaldehyde did not provide the desired alcohol **45**. Instead, compound **45** was prepared via a triisopropylsilyl-imidazole derivative following a published procedure.¹⁰ Compounds **40** and **45** give the respective substitution products (**42** and **46**) from reactions at 25 °C in $\text{CF}_3\text{SO}_3\text{H}$ and C_6H_6 . In the case of compound **40**, it ionizes to the 1,3-dication (**41**) and then mainly reacts with benzene to give **42**. Only minor amounts of the rearrangement product (**44**) could be detected by GC–MS. If the imidazole substrates (**40** and **45**) are reacted in superacid and allowed to equilibrate (1 h at 50 °C) and the benzene is subsequently added, then the respective charge rearrangement products (**44** and **47**) are formed as major products. Thus for ionization of **40**, the 1,3-dication (**41**) isomerizes to the 1,4-dication (**43**) and the charge-separated dication reacts with benzene. Unfortunately, high yields of the rearranged products (**44** and **47**) are precluded by their decomposition in heated superacid.



The superacid-promoted acyl-transfer reactions of imidazoles have also been studied. Previous work by Keumi and co-workers demonstrated that *N*-acylimidazoles were capable of acylating electron-rich aromatic compounds in $\text{CF}_3\text{CO}_2\text{H}$ solution.¹¹ However, using $\text{CF}_3\text{CO}_2\text{H}$, *N*-benzoylimidazole did not react with benzene and produced only a 5% yield of benzoylated product from toluene (2- and 4-methylbenzophenone). We have found that *N*-acetylimidazole (**48a**) and *N*-benzoylimidazole (**48b**) react with benzene in $\text{CF}_3\text{SO}_3\text{H}$ solution to give the corresponding Friedel–Crafts products (eq 8). In the earlier studies by Keumi, a mechanism was proposed involving the

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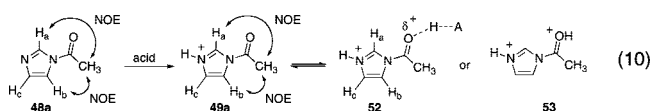
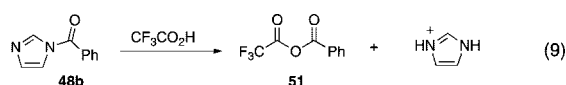
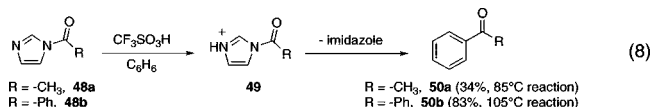
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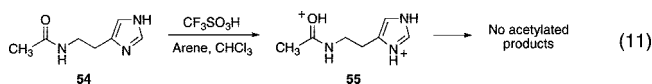
formation of mixed anhydrides (i.e., **51**) from $\text{CF}_3\text{CO}_2\text{H}$ and the *N*-acetylimidazole (**48b**). It was further suggested that **51** is the active acyl-transfer agent from **48b** in $\text{CF}_3\text{CO}_2\text{H}$. In order to gain further mechanistic insights, *N*-acetylimidazole (**48a**) was dissolved in $\text{CF}_3\text{CO}_2\text{H}$ and $\text{CF}_3\text{SO}_3\text{H}$ solutions and studied by ^1H NMR using NOE experiments.¹² Compound **48a** exhibits prominent NOE enhancements between H_a , H_b , and the methyl group in CDCl_3 solution. In $\text{CF}_3\text{CO}_2\text{H}$ and $\text{CF}_3\text{SO}_3\text{H}$ solutions, ion **49a** initially shows the same NOE enhancements. The $\text{CF}_3\text{SO}_3\text{H}$ solution of **49a** was found to be indefinitely stable, with no new imidazole/acetyl signals observed in the NMR and no diminished NOE effects (at 25 and 50 °C). However, the $\text{CF}_3\text{CO}_2\text{H}$ solution of **49a** degraded rapidly with new imidazole/acetyl signals forming in the ^1H NMR. Within 24 h at 50 °C, only about 10% of the **49a** remained in the $\text{CF}_3\text{CO}_2\text{H}$ solution, and the new imidazole/acetyl signals did not exhibit NOE enhancements.



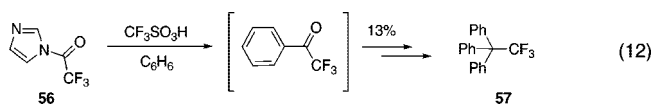
These results suggest divergent mechanisms for acetyl-transfer reactions involving **48a**, depending on the acid strength. In $\text{CF}_3\text{CO}_2\text{H}$, NOE experiments clearly show that *N*-acetylimidazole (**48a**) is cleaved in the mildly acidic solution (H_0 -2.7). This can occur as a result of the relatively strong nucleophile strength of the trifluoroacetate anion, allowing for nucleophilic attack on the imidazolium ion **49** and formation of the mixed anhydride (similar to **51**). The mixed anhydride may then react with activated, electron-rich arenes. However, triflic acid is a much stronger Brønsted acid, and the triflate anion is a considerably weaker nucleophile (compared to the trifluoroacetate anion), so formation of a mixed anhydride is prevented. The NOE experiments also argue against the involvement of a free acetyl cation (CH_3CO^+) or its protosolvated superelectrophile ($\text{CH}_3\text{COH}^{2+}$), because these ionizations would lead to diminished NOE effects in the ^1H NMR spectra. Thus, superacid-promoted acyl transfer to benzene involves either the imidazolium ion **49a** or, perhaps more likely, one of the superelectrophilic derivatives **52** or **53**.

A histamine derivative (**54**) was also studied for its tendency to undergo acyl-transfer reactions with arene nucleophiles. In reactions with benzene, toluene, or naphthalene, in $\text{CF}_3\text{SO}_3\text{H}$, there are no acetylated arenes formed (eq 11). On the basis of the acid strength of $\text{CF}_3\text{SO}_3\text{H}$ (H_0 -14.1), it is likely that both the imidazole and amide groups are fully protonated. However, dication **55** is not sufficiently electrophilic to acetylate the arenes. Although amides are generally not reactive in Friedel–

Crafts acylation reactions, it has been shown that superelectrophilic amides may undergo acyl transfer to benzene and other arenes.¹³ In the present case, the imidazolium cation is too distant from the (protonated) amide to generate the necessary superelectrophilic activation for acyl transfer to the arenes.



The *N*-(trifluoroacetyl)imidazole (**56**) was also studied in superacidic reactions with benzene. Upon reaction of compound **56** with $\text{CF}_3\text{SO}_3\text{H}$ and C_6H_6 (24 h at 25 °C), the only significant product was determined to be 1,1,1-trifluoro-2,2,2-triphenylethane (**57**, eq 12). This product is the result of an initial acyl-transfer reaction to benzene to give 2,2,2-trifluoroacetophenone. Further reaction at the carbonyl provides compound **57**, a known conversion of 2,2,2-trifluoroacetophenone in triflic acid.¹⁴ Product **57** is formed in low yield (13%), likely a consequence of the low basicity of **56** and its inability to form the superelectrophilic carboxonium ion.



Conclusion

We have found evidence that the imidazolium ion can significantly enhance the reactivities of adjacent electrophilic centers (i.e., carboxonium ions). This may be an important structure–reactivity element in some imidazole-based compounds. In superacidic reactions, imidazole-based superelectrophiles may be involved in the conversions. The high reactivities of imidazole-based superelectrophiles can be exploited in synthetic methodologies leading to functionalized imidazole products.

Experimental Section

Trifluoromethanesulfonic acid was obtained from a commercial supplier and distilled under an Ar atmosphere prior to use. The imidazolecarboxaldehydes **1**–**4**, ketone **17**, and other reagents/solvents were obtained from commercial suppliers. Imidazole **5** was prepared using a published procedure,¹⁵ and imidazoles **40** and **45** were prepared using a modified literature procedure.¹⁰ ^1H and ^{13}C NMR spectra were recorded on a 500 MHz NMR spectrometer, and low-resolution mass spectra were obtained from a capillary GC (DB-5 column) equipped with a mass selective detector.

General Procedure A for the Condensations of Imidazole Alcohols, Aldehydes, and Ketones with Arenes. The imidazole substrate (0.1 g) is dissolved in benzene (or other arene; 1.0 mL) and $\text{CF}_3\text{SO}_3\text{H}$ (1–2 mL) is added. The reaction is stirred at least 2 h, and then the mixture is poured over several grams of ice. The mixture is made basic (pH paper) with the slow addition of 10 M NaOH. The resulting solution is extracted twice with CHCl_3 , and the combined organic extracts are further washed with water (once) and then brine (twice). If purification is necessary, the product mixture is subjected to column chromatography (silica gel; hexane/ether).

(12) If the *N*-acetylimidazole (**48a**) is dissolved in $\text{CF}_3\text{SO}_3\text{H}$ at 25°C, roughly 10% of the **48a** undergoes an immediate cleavage reaction, while the remaining **49a** remains stable under the reaction conditions. If **48a** is slowly and carefully added to $\text{CF}_3\text{SO}_3\text{H}$ at -30°C, then no cleavage products are observed. Presumably, solvation of **48a** at 25°C can generate intense localized heating, which leads to some cleavage of **48a** or **49a** (even in $\text{CF}_3\text{SO}_3\text{H}$).

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2-Benzhydryl-1-methyl-1H-imidazole (6). Using general procedure A, compound **1** is reacted with C₆H₆ and CF₃SO₃H. Product **6** is isolated. ¹H NMR (CDCl₃): δ 3.47 (s, 3H), 5.51 (s, 1H), 6.87 (s, 1H), 7.05 (s, 1H), 7.20–7.35 (m, 10H). ¹³C NMR (CDCl₃): δ 32.9, 49.5, 121.0, 126.9, 127.6, 128.6, 128.9, 141.0, 148.7. Low resolution MS (EI): 248 (M⁺), 247, 165. High resolution MS (EI), C₁₇H₁₆N₂ calcd: 248.13135, found 248.13070.

5-Benzhydryl-4-methyl-1H-imidazole (8). Using general procedure A, compound **3** is reacted with C₆H₆ and CF₃SO₃H. Product **8** is isolated. ¹H NMR (CDCl₃): δ 2.07 (s, 3H), 5.39 (s, 1H), 7.10–7.44 (m, 10), 11.7 (m, 1H). ¹³C NMR (CDCl₃): δ 10.0, 48.3, 126.2, 128.4, 129.2, 133.7, 122.5, 145.1. Low resolution MS (EI): 248 (M⁺), 247, 233, 171. High resolution MS (EI), C₁₇H₁₆N₂ calcd: 248.13135, found 248.13140.

5-(Bis(2,4-dichlorophenyl)methyl)-4-methyl-1H-imidazole (9). Using general procedure A, compound **3** is reacted with 1,3-dichlorobenzene and CF₃SO₃H. Product **9** is isolated. ¹H NMR (CDCl₃): δ 2.11 (s, 1H), 5.98 (s, 1H), 7.08–7.16 (m, 4H), 7.39 (s, 3H). ¹³C NMR (CDCl₃): δ 9.8, 41.7, 127.0, 129.4, 131.2, 133.1, 133.5, 134.7, 138.3. Low resolution MS (EI): 388/386/384 (M⁺), 351/349, 313, 239. High resolution MS (EI), C₁₇H₁₂Cl₄N₂ calcd: 383.97545, found 383.97563.

1-Methyl-2-(1,1-diphenylethyl)-1H-imidazole (11). Using general procedure A, compound **5** is reacted with C₆H₆ and CF₃SO₃H. Product **11** is isolated. ¹H NMR (CDCl₃): δ 2.23 (s, 1H), 2.90 (s, 3H), 6.78 (d, *J* = 1.0 Hz, 1H), 7.06 (d, *J* = 1.0 Hz, 1H), 7.14–7.31 (m, 10H). ¹³C NMR (CDCl₃): δ 32.7, 34.9, 50.6, 122.7, 126.5, 126.6, 127.9, 128.4, 145.0, 152.0. Low resolution MS (EI): 262 (M⁺), 261, 246, 171, 103. High resolution MS (EI), C₁₈H₁₈N₂ calcd: 262.1470, found 262.1470.

General Procedure B for the Intramolecular Cyclizations of Imidazole Alcohols and Olefins. The imidazole substrate (1 mmol) is dissolved in CHCl₃, and CF₃SO₃H (3 mL, 33 mmol) is added. Depending on the substrate the solution may be heated. The reaction is stirred at least 2 h and then poured over several grams of ice. The mixture is made basic (pH paper) with the slow addition of 10 M NaOH. The resulting solution is extracted twice with CHCl₃, and the combined organic extracts are further washed with water (once) and then brine (twice). If purification is necessary, the product mixture is subjected to column chromatography (silica gel; hexane/ether).

1-Phenylimidazo[5,1-*a*]isoquinoline (23). 4,5-Diphenylimidazole (0.5 g, 2.3 mmol) is dissolved in 20 mL of anhydrous THF, KOtBu (0.26 g, 2.3 mmol) is added, and the mixture is stirred at 25 °C for 1 h. To this mixture is added dropwise a styrene oxide (0.3 g, 2.5 mmol) solution in 10 mL of THF, and the final solution is then refluxed for 1 h. The product mixture is then diluted with water and extracted three times with ether. The combined organic extracts are then washed three times with brine solution, dried over anhydrous Na₂SO₄, and concentrated by removal of the solvent. Further purification is achieved by column chromatography (silica gel; hexane/ether/NH₄OH (trace)). The 2-(4,5-diphenyl-1H-imidazol-1-yl)-1-phenylethanol (**20**) is reacted with CF₃SO₃H according to general procedure B. Compound **23** is isolated. ¹H NMR (CDCl₃): δ 6.82 (d, *J* = 7.3 Hz, 1H), 7.31–7.35 (m, 1H), 7.38–7.41 (m, 1H), 7.43–7.45 (m, 1H), 7.51–7.58 (m, 3H), 7.75–7.78 (m, 3H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.14 (s, 1H). ¹³C NMR (CDCl₃): δ 114.3, 121.0, 122.6, 123.1, 125.5, 127.0, 127.3, 127.7, 127.9, 128.0, 128.6, 129.6, 135.5, 136.4. Low resolution MS (EI): 244 (M⁺), 243, 216, 189, 108. High resolution MS (EI), C₁₇H₁₂N₂ calcd: 244.09979, found 244.10005.

6-Phenyl-5,6-dihydroimidazo[2,1-*a*]isoquinoline (25). Similar to the preparation of compound **20**, 2-phenylimidazole is reacted with styrene oxide to prepare 1-phenyl-2-(2-phenyl-1H-imidazol-1-yl)ethanol (**24**). Compound **24** is reacted with CF₃SO₃H according to general procedure B. Product **25** is isolated. ¹H NMR (CDCl₃): δ 4.22 (dd, *J* = 7.6, 12.4 Hz, 1H), 4.32 (dd, *J* = 5.7, 12.4 Hz, 1H), 4.39 (m, 1H), 6.82 (s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 7.15 (s, 1H), 7.20–7.23 (m, 1H), 7.25–7.28 (m, 3H), 7.34–7.37 (m, 1H), 8.14 (d, *J* = 7.7 Hz, 1H). ¹³C NMR (CDCl₃):

δ 44.7, 49.9, 119.3, 123.6, 127.1, 127.5, 127.9, 128.2, 128.3, 128.6, 128.9, 129.4, 135.4, 140.8, 144.1. Low resolution MS (EI): 246 (M⁺), 245, 169, 128. High resolution MS (EI), C₁₇H₁₄N₂ calcd: 246.1157, found 246.1153.

6-Methyl-1-phenyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (29). 4,5-Diphenylimidazole (0.5 g, 2.2 mmol) is dissolved in 20 mL of anhydrous ether, and KOtBu (0.27 g, 2.4 mmol) is then added at 25 °C. The mixture is stirred at 25 °C for 30 min, and then allyl bromide (0.2 mL, 2.3 mmol) is added. After 30 min of stirring, the solution is partitioned between ether and water. The organic phase is then washed twice with brine and dried over magnesium sulfate. Further purification is achieved by column chromatography (silica gel; hexane/ether). The 1-allyl-4,5-diphenyl-1H-imidazole (**27**) is reacted with CF₃SO₃H according to general procedure B. Product **29** is isolated. ¹H NMR (CDCl₃): δ 1.35 (d, *J* = 7.0 Hz, 3H), 3.22–3.29 (m, 1H), 3.91 (dd, *J* = 12.2, 5.7 Hz, 1H), 4.14 (dd, *J* = 12.2, 4.4 Hz, 1H), 7.12–7.15 (m, 1H), 7.20–7.23 (m, 1H), 7.29–7.31 (m, 1H), 7.33–7.36 (m, 1H), 7.41–7.44 (m, 2H), 7.60 s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.74–7.76 (m, 2H). ¹³C NMR (CDCl₃): δ 18.1, 34.1, 48.4, 123.6, 124.3, 126.7, 127.0, 127.2, 127.3, 128.4, 128.4, 135.7, 135.7, 137.2, 138.0, 143.6. Low resolution MS (EI): 260 (M⁺), 259, 218, 115. High resolution MS (EI), C₁₈H₁₆N₂ calcd: 260.13135, found 260.13086.

6-Methyl-5,6-dihydroimidazo[2,1-*a*]isoquinoline (32). Similar to the procedure for compound **25**, 1-allyl-2-phenyl-1H-imidazole (**30**) is prepared by reaction of 2-phenylimidazole and allyl bromide and it is reacted with CF₃SO₃H according to general procedure B. Product **32** is isolated. ¹H NMR (CDCl₃): δ 1.33 (d, *J* = 7.0 Hz, 3H), 3.27–3.31 (m, 1H), 3.91 (dd, *J* = 12.4, 5.9 Hz, 1H), 4.21 (dd, *J* = 12.4, 5.1 Hz, 1H), 6.94 (s, 1H), 7.17 (s, 1H), 7.27–7.37 (m, 3H), 8.05–8.07 (m, 1H). ¹³C NMR (CDCl₃): δ 19.0, 33.2, 49.6, 119.3, 123.7, 126.3, 126.4, 127.5, 128.6, 129.2, 137.6, 143.9. Low resolution MS (EI): 184 (M⁺), 169, 128, 84. High resolution MS (EI), C₁₂H₁₂N₂ calcd: 184.1001, found 184.0996.

1-(2-(2,4-Dichlorophenyl)-2-phenylethyl)-1H-imidazole (35). Miconazole nitrate salt (0.2 g, 4.2 mmol) is suspended in 4 mL of CHCl₃, and the solution is washed with 1.0 M NaOH and then brine. The chloroform solution is then dried over MgSO₄, filtered, and added directly to a solution of C₆H₆ (1 mL) and CF₃SO₃H (3 mL) with stirring. After stirring at 25 °C for 4 h, the reaction is worked up according to general experimental procedure A. Compound **35**: ¹H NMR (CDCl₃): δ 4.58 (d, *J* = 7.8 Hz, 2H), 4.86 (t, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 6.99 (s, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.25–7.33 (m, 5H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.49 (m, 1H). ¹³C NMR (CDCl₃): δ 48.1, 51.0, 119.1, 127.6, 127.7, 128.0, 128.5, 129.0, 129.2, 130.0, 133.7, 135.0, 136.8, 137.2, 138.8. Low resolution MS (EI): 283/281 (M-35/37), 235/237, 165. High resolution MS (EI), C₁₇H₁₄N₂Cl₂ calcd: 316.0534, found 316.0536.

2-(1,2-Diphenylethyl)-1-methyl-1H-imidazole (42). Using general procedure A, compound **40** is reacted to give product **42** as the major product. Compound **42**: ¹H NMR (CDCl₃): δ 3.26 (s, 3H), 3.29 (dd, *J* = 13.4, 8.0 Hz, 1H), 3.75 (dd, *J* = 13.4, 8.1 Hz, 1H), 4.14–4.17 (m, 1H), 6.75 (s, 1H), 7.03 (d, *J* = 7.0 Hz, 2H), 7.06 (s, 1H), 7.13–7.29 (m, 8H). ¹³C NMR (CDCl₃): δ 32.4, 42.2, 46.1, 120.8, 126.1, 126.7, 127.1, 128.0, 128.1, 128.5, 129.3, 140.1, 141.3, 149.1. Low resolution MS (EI): 262 (M⁺), 171, 130. High resolution MS (EI), C₁₈H₁₈N₂ calcd: 262.14700, found 262.14696.

2-(2,2-Diphenylethyl)-1-methyl-1H-imidazole (44). Using general procedure A (modified by dissolving **40** in CHCl₃, heating to 50 °C for 1 h, and then adding C₆H₆), compound **40** is reacted to give product **44** as the major product. Compound **44**: ¹H NMR (CDCl₃): δ 3.05 (s, 3H), 3.38 (d, *J* = 7.7 Hz, 2H), 4.65 (t, *J* = 7.7 Hz, 1H), 6.44 (s, 1H), 6.98 (s, 1H), 7.17–7.21 (m, 6H), 7.26–7.29 (m, 4H). ¹³C NMR (CDCl₃): δ 32.0, 33.3, 50.1, 120.0, 126.3, 127.5, 128.0, 128.3, 144.0, 146.7. Low resolution MS (EI): 262 (M⁺), 167, 95. High resolution MS (EI), C₁₈H₁₈N₂ calcd: 262.1470, found 262.1469.

5-(1,2-Diphenylethyl)-1-methyl-1H-imidazole (46). Using general procedure A, compound **45** is reacted to give product **46** as the major product. Compound **46**: ¹H NMR (CDCl₃): δ 3.13 (dd, *J* =

13.4, 8.8, 1H), 3.19 (s, 3H), 3.44 (dd, $J = 13.4, 6.4$, 1H), 4.88 (dd, $J = 8.7, 6.5$ Hz, 1H), 6.98–7.00 (m, 4H), 7.16–7.22 (m, 7H), 7.34 (s, 1H). ^{13}C NMR (CDCl_3): δ 31.3, 42.3, 44.3, 126.2, 126.7, 128.0, 128.1, 128.5, 129.1, 134.1, 138.1, 139.3, 141.8. Low resolution MS (EI): 262 (M^+), 171, 103. High resolution MS (EI), $\text{C}_{18}\text{H}_{18}\text{N}_2$ calcd: 262.1470, found 262.1467.

5-(2,2-Diphenylethyl)-1-methyl-1H-imidazole (47). Using general procedure A (modification: dissolved **45** in CHCl_3 , heated to 50 °C for 1 h, and then added C_6H_6), compound **45** is reacted to give product **47** as the major product. Compound **47**: ^1H NMR (CDCl_3): δ 3.34 (d, $J = 19.3$ Hz, 2H), 3.49 (s, 3H), 4.27 (t, $J = 19.3$ Hz, 1H), 6.70 (s, 1H), 7.14–7.40 (m, 10H), 8.18 (s, 1H). ^{13}C NMR (CDCl_3): δ 29.7, 30.4, 51.4, 126.6, 127.8, 128.3, 128.5, 143.8. Low resolution MS (EI): 262 (M^+), 167, 152, 95. High resolution MS (EI), $\text{C}_{18}\text{H}_{18}\text{N}_2$ calcd: 262.1470, found 262.1465.

Acknowledgment. Grateful acknowledgement is made to the donors of the American Chemical Society Petroleum Research Fund (PRF 44697-AC1), the National Science Foundation (CHE-0749907), and the Department of Chemistry and Biochemistry at Northern Illinois University for support of this work; this research was conducted in part by the students of the CHEM 339 laboratory class.

Supporting Information Available: NMR spectra of new compounds, experimental procedures, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO802798X