Electrophilic Activation of Acetyl-Substituted Heteroaromatic Compounds

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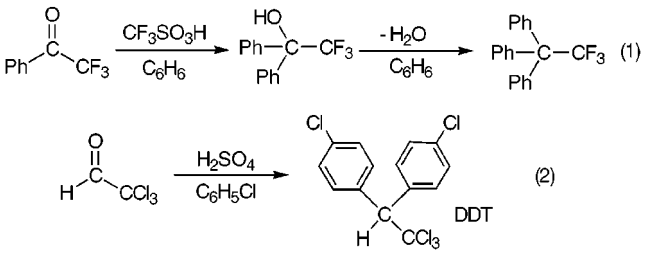
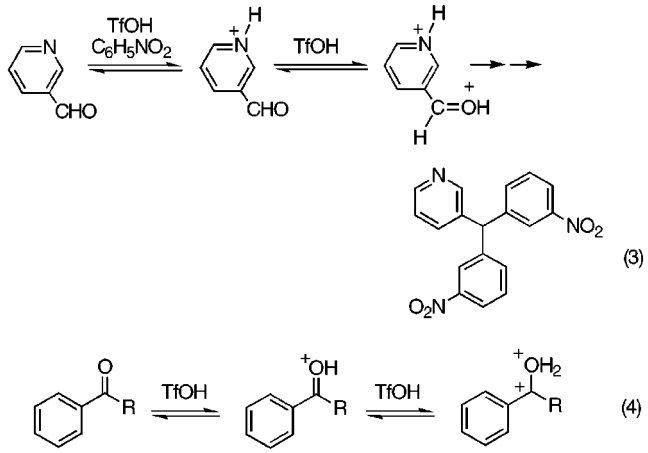
The chemistry of acetyl-substituted pyridines, thiazoles, quinoline, isoquinolines, and pyrazine (**1**−**9** and **28**) has been studied. These heteroarenes (**1**−**8**) condense with benzene in good yields (74−96%) in the Bronsted superacid, CF_3SO_3H (triflic acid). In these acid-catalyzed hydroxyalkylation reactions, compounds **1**−**8** are significantly more reactive than acetophenone. It is proposed that compounds **1**−**8** readily form dicationic electrophiles in triflic acid.

Introduction

The acid-catalyzed condensation of ketones and aldehydes with aromatic compounds is known as the hydroxyalkylation reaction.[1] This widely used reaction has been applied to the preparation of plastics (phenol−formaldehyde resins),[2] dyes and pigments (for example, malachite green),[3] and other products such as porphyrins.[4] The hydroxyalkylation reaction is useful when electron-rich arenes are condensed with the ketone or aldehyde. With less reactive aromatic compounds such as benzene or chlorobenzene, the ketone or aldehyde must have a strong electron-withdrawing group in order for the condensation to take place. For example, 2,2,2-trifluoroacetophenone condenses with benzene in CF_3SO_3H (triflic acid, TfOH), and DDT is prepared by the acid-catalyzed condensation of chloral or its hydrate with chlorobenzene (eqs 1−2).[5,6]



Recently, there has been significant interest in the chemistry of dicationic and superelectrophilic species.[7] In hydroxyalkylation reactions catalyzed by Bronsted superacids, very high reactivity has been observed for some aldehydes and ketones, and this has been attributed to the formation of dicationic electrophiles (eq 3).[8] The dicationic electrophiles can be formed by either of two routes: by protonation of the carbonyl group along with an adjacent base-site (eq 3)[8,9] or by double protonation of the carbonyl group (eq 4).[10] Given the value of this



synthetic chemistry, we have been exploring the scope and utility of these methods of electrophilic activation in hydroxyalkylation reactions. In the following paper, we report our studies of the hydroxyalkylation reaction involving acetyl-substituted heteroarenes and related systems.

(1) (a) Hofmann, J. E.; Schriesheim, A. In *Friedel−Crafts and Related Reaction*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol 2, pp 597−640. (b) March, J. *Advanced Organic Chemistry*, 4th ed; Wiley: New York, 1992; pp 548−549.

(2) Chenier, P. J. *Handbook of Industrial Chemistry*, 2nd ed.; VHC: New York, 1992; p 293.

(3) (a) Krahler, S. E. In *The Chemistry of Synthetic Dyes and Pigments*; Lubs, H. A., Ed.; Krieger Publishing Co.: Malabar, FL, 1955; p 275. (b) *Colour Index*, 3rd Ed; 1971; Vol. 4, p 4380.

(4) (a) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978. For recent examples, see: (b) Kral, V.; Sessler, J. L.; Zimmerman, R. S.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1055. (c) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084

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(7) (a) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767. (b) *Stable Carbocation Chemistry*; Prakash, G. K. S., Schleyer, P. v. R., Eds.; Wiley: New York, 1997. (c) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611.

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(10) (a) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081. (b) Saito, S.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1996**, *61*, 8089.

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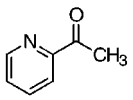
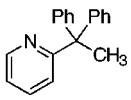
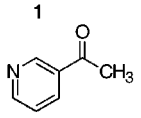
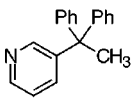
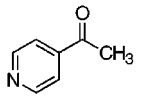
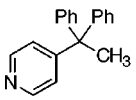
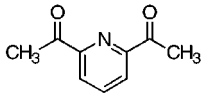
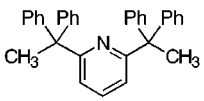
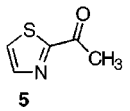
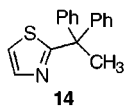
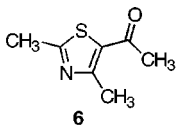
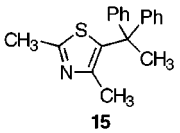
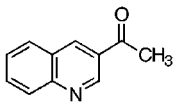
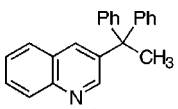
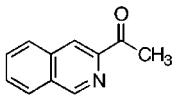
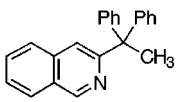
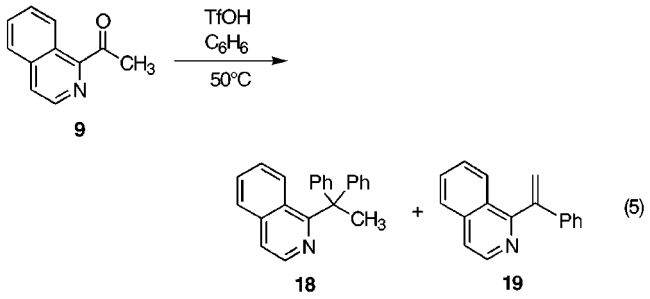
Table 1. Results from the Reaction of Acetyl-Substituted Arenes (1−9) with Benzene in CF_3SO_3H

Starting Material	Product	% Yield
 1	 10	93 %
 2	 11	88 %
 3	 12	96 %
 4	 13	90 %
 5	 14	75 %
 6	 15	91 %
 7	 16	80 %
 8	 17	74 %

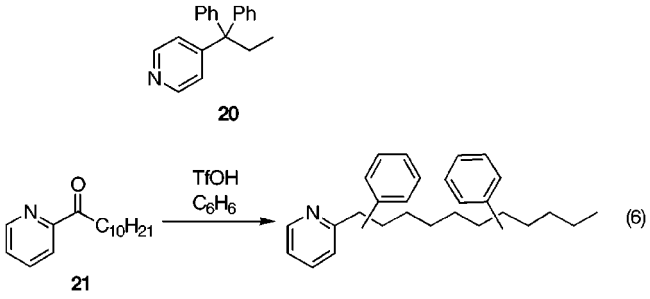
Results and Discussion

Although it has been reported that acetophenone is unreactive toward benzene in TfOH,[11] the acetylpyridines (**1**−**3**) give the respective condensation products (**10**−**12**) in excellent yields (Table 1). Compounds similar to **10**−**12** are known to have fungicidal activity,[12] estrogen synthetase inhibitory activity,[13] and other biological activities.[14] To our knowledge, the only other published synthetic route to compounds **10**−**12** involves the deprotonation and alkylation of diphenylpyridylmethanes.[15] The sterically crowded pyridine **13** is also prepared in good yield from 2,6-diacetylpyridine (**4**). The acetyl-substituted thiazoles (**5** and **6**), quinoline (**7**), and isoquinoline (**8**) likewise give the respective condensation products **14**−**17**.

With prolonged reaction time and heating, isoquinoline **9** does give a trace quantity of **18**, but the major product is **19** (isolated in 57% yield, eq 5). When a pure sample



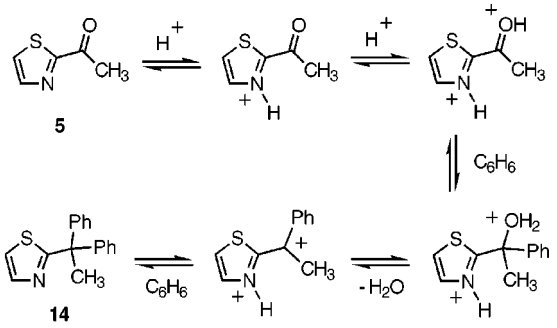
of **18** is reacted with TfOH and C_6H_6 at 50 °C, only product **18** is observed in the resulting product mixture. This suggests that the product distribution for 1-acetylisoquinoline (**9**) is the result of a kinetically controlled reaction. Reaction with the second C_6H_6 may be inhibited by unfavorable steric effects arising from the peri position. In addition to acetyl-substituted heteroaromatics, some acyl-substituted heteroarenes condense with C_6H_6 in TfOH. Compound **20** is prepared in 94% yield from 4-propionylpyridine, but reaction of **21** gives a mixture of at least 6 diphenylated products (eq 6). The product mixture suggests that intramolecular hydride transfer(s) may be involved and that the resulting cationic intermediates give the mixture of products.



The above results suggest an obvious question: why is the acetyl group of acetophenone unreactive toward benzene in superacid, but the analogous heteroaromatic compounds react in good to excellent yields? In the case of acetophenone, the carbonyl group is fully protonated in TfOH,[16] but the resulting carboxonium ion is stabilized by inductive and resonance effects. Shudo and Ohwada have reported kinetic evidence for diprotonation of aryl ketones;[16] however, diprotonated intermediates from acetophenone must be formed in extremely low concentration. Thus, acetophenone is unreactive toward benzene in the hydroxyalkylation reaction catalyzed by TfOH. The acetyl-substituted heteroarenes possess strong base-sites which are fully protonated in acid, so that upon subsequent protonation of the carbonyl groups, reactive dicationic electrophiles can be generated (Scheme 1). We propose that the reactivity of the heteroaromatic compounds stems from their ability to form appreciable concentrations of the diprotonated electrophiles. The enhanced reactivity of dicationic electrophiles was first

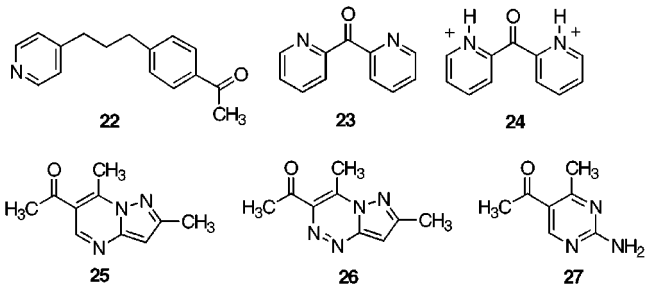
(11) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *116*, 1364.
(12) Whaley, J. W.; Taylor, H. M. *Phytopathology* **1970**, *60*, 771.
(13) Jones, C. D.; Winter, M. A.; HIrsch, K. S.; Stamm, N.; Taylor, H. M.; Holden, H. E.; Davenport, J. D.; Krumkalns, E. V.; Suhr, R. G. *J. Med. Chem.* **1990**, *33*, 416.
(14) Franklin, M. R. *J. Pharmacology* **1993**, *46*, 683.
(15) (a) Martensson, O.; Nilsson, E. *Acta Chem. Scand.* **1961**, *15*, 1021. (b) Eisch, J. J.; Kovacs, C. A.; Chobe, P.; Boleslawski, M. P. *J. Org. Chem.* **1987**, *52*, 4427
(16) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312.

Scheme 1



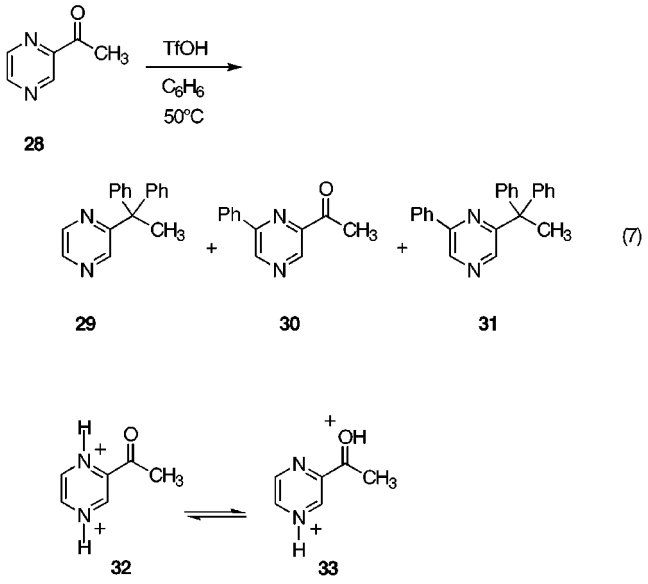
recognized by Olah and co-workers, and it is thought to be the result of electrostatic and inductive effects.[17,7a]

In addition to the acetyl-substituted arenes **1**−**9**, ketones **22**, **23**, and **25**−**27** were reacted under similar conditions. The substituted acetophenone (**22**) does not condense with benzene in TfOH and it can be recovered quantitatively. Although diprotonated species are likely formed from **22** in superacid, the protonated acetyl group is not sufficiently electrophilic to react with benzene. This seems to suggest that dicationic electrophiles only show high reactivity when the charge centers are conjugated or in close proximity. When ketone **23** is reacted with benzene in TfOH, the condensation does not occur and compound **23** can also be recovered. Protonation must only occur at the pyridyl rings (**24**) and consequently no reaction occurs at the carbonyl group. In general, heteroarenes having more than one strong base-site were unreactive to the condensation chemistry. Even at elevated temperature, compounds **25**−**27** do not condense with C_6H_6 in TfOH.

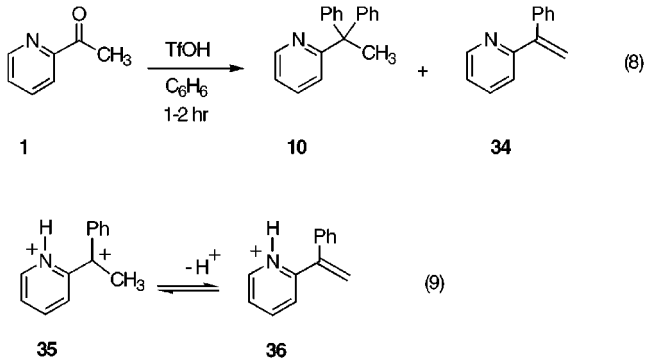


Despite having two base sites on the heterocyclic ring, acetylpyrazine (**28**) does condense with C_6H_6 in TfOH (eq 7). Product **29** is formed, which suggests an equilibrium between intermediates **32** and **33** in TfOH. Product **30** is formed as the other major product from **28**. When the reaction is conducted at elevated temperature (50 °C), product **31** is also formed as a minor product. It is not presently clear how the pyrazine ring is phenylated to give **30** and **31**, but further studies are in progress.

The condensation of 2-acetylpyridine (**1**) with C_6H_6 can be accomplished in 4 h at 25 °C using an excess of TfOH (14 equiv). When lower quantities of TfOH or shorter reaction times are used, the condensation product is accompanied by significant quantities of compound **34** (eq 8). An equilibrium is likely established between **35** and **36** (eq 9). With highly acidic conditions and longer reactions, **35** is formed and this leads to product **10**.



2-Acetylpyridine (**1**) also condenses with toluene and chlorobenzene, but despite high yields for these conversions, the reactions occur with poor regioselectivities. No reaction is seen with *o*-dichlorobenzene or nitrobenzene even when **1** is reacted with a large excess of TfOH at 80 °C. When **1** is reacted with C_6H_6 and a large excess of H_2SO_4 (100 h at 50 °C), no reaction is seen. This is consistent with the proposed mechanism for the hydroxyalkylation reactions (Scheme 1). Superacidic conditions are required because weaker acids such as H_2SO_4 are unable to generate diprotonated intermediates.



Conclusion

We have found that acetyl-substituted pyridines, thiazoles, quinoline, isoquinoline, and pyrazine condense with benzene in hydroxyalkylation reactions in the Bronsted superacid, CF_3SO_3H. These acetylheteroarenes are significantly more reactive than acetophenone in the hydroxyalkylation reaction. Due to inductive and electrostatic effects, the protonated heteroaromatic rings contribute significantly to the electrophilic activation of carboxonium ion intermediates.

Experimental Section

Triflic acid was purchased from 3M Co. and distilled under an inert atmosphere immediately prior to use.[18] The acetyl-substituted arenes were purchased from commercial suppliers

(17) (a) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. *J. Am. Chem. Soc.* **1975**, *97*, 3928. (b) Olah, G. A.; Hartz, N.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1993**, *115*, 6985.

(18) (a) For a review of TfOH chemistry, see: Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15. (b) Olah, G. A.; Prakash, G. K. S.; Sommer, J. In *Superacids*; Wiley: New York, 1985. (c) TfOH may be quantitatively recycled; for a procedure, see: Booth, B. L.; El-Fekky, T. A. *JCS Perkin I* **1979**, 2441.

and used as received. Compound **7** was prepared by the reaction of CH_3MgBr with 4-quinolinecarboxaldehyde and subsequent oxidation with SeO_2. Compound **8** was prepared by the reaction of CH_3MgBr with 2-isoquinolinecarbonitrile; compound **21** was prepared by the reaction of 1-decylmagnesium bromide with 2-pyridinecarbonitrile. Compound **22** was prepared by acylation of 4-(3-phenylpropyl)pyridine using $AlCl_3$ and acetyl chloride.[19] High-resolution mass spectra were recorded at the Mass Spectrometry Facility at the University of California, Riverside. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 125 MHz. All NMR spectra were recorded from $CDCl_3$ solutions.

General Procedure for the Preparation of Condensed Products 10−19. A 0.2 g portion of the acetyl-substituted heteroarene was dissolved in 1.0 mL of C_6H_6, and to this solution was added 5.0 mL of triflic acid. This mixture was stirred at room temperature (**6** was reacted at 50 °C) for 4−12 h and then poured over several grams of ice. The resulting solution was made basic with concentrated NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O and brine and then dried with $MgSO_4$. Removal of the solvent under reduced pressure then provided the product. The product(s) was then purified by recrystallization or column chromatography.

2-(1,1-Diphenylethyl)pyridine (10): mp 51−54 °C ($CHCl_3$, lit.[15a] mp 54−56 °C); ^1H NMR δ 2.27 (s, 3H), 7.01 (d, J = 8.1 Hz, 1H), 7.11−7.15 (m, 4H), 7.20−7.32 (m, 7H), 7.55 (dt, J = 1.8, 7.5, 1H), 8.65 (m, 1H); ^{13}C NMR δ 29.4, 55.1, 121.0, 123.6, 126.9, 128.0, 128.6, 135.8, 148.3, 148.9, 167.1; EI MS 259 (M^+); HRMS *m/z* calcd for $C_{19}H_{17}N$ 259.1361, found 259.1369.

3-(1,1-Diphenylethyl)pyridine (11): mp 108−110 °C ($CHCl_3$); ^1H NMR δ 2.21 (s, 3H), 7.07−7.10 (m, 4H), 7.18−7.32 (m, 7H), 7.38 (m, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.46 (dd, J = 1.2, 4.5 Hz, 1H); ^{13}C NMR δ 30.2, 51.1, 122.7, 126.3, 128.1, 128.5, 136.1, 144.4, 147.2, 147.8, 150.1; EI MS 259 (M+); HRMS *m/z* calcd for $C_{19}H_{18}N$ (MH^+) 260.1439, found 260.1430.

4-(1,1-Diphenylethyl)pyridine (12): mp 87−90 °C ($CHCl_3$); ^1H NMR δ 2.17 (s, 3H), 7.02−7.10 (m, 6H), 7.25−7.31 (m, 6H), 8.50 (d, J = 6.0 Hz, 1H); ^{13}C NMR δ 29.7, 52.3, 123.8, 126.4, 128.1, 128.5, 147.2, 149.5, 157.9; EI MS 259 (M^+); HRMS *m/z* calcd for $C_{19}H_{17}N$ 259.1361, found 259.1358.

2,6-Bis-(1,1-diphenylethyl)pyridine (13): mp 138−140 °C ($CHCl_3$); ^1H NMR δ 2.13 (s, 6H), 6.84 (d, J = 7.8 Hz, 2H), 7.06−7.10 (m, 8H), 7.18−7.26 (m, 12H), 7.40 (t, J = 7.8, 1H); ^{13}C NMR δ 29.2, 55.2, 120.0, 125.6, 127.5, 128.7, 135.7, 148.7, 165.2; EI MS 439 (M+); HRMS *m/z* calcd for $C_{33}H_{28}N$ (M − H) 438.2222, found 438.2212.

2-(1,1-Diphenylethyl)thiazole (14): mp 46−48 °C ($CHCl_3$); ^1H NMR δ 2.29 (s, 3H), 7.16−7.20 (m, 4H), 7.23−7.32 (m, 7H), 7.82 (d, J = 3.3 Hz, 1H). ^{13}C NMR δ 29.8, 53.4, 119.3, 126.8, 128.1, 128.1, 142.5, 147.6, 178.9; EI MS 265 (M^+); HRMS *m/z* calcd for $C_{17}H_{15}NS$ 265.0925, found 265.0930.

2,4-Dimethyl-5-(1,1-diphenylethyl)thiazole (15): mp 58−61 °C ($CHCl_3$); ^1H NMR δ 1.90 (s, 3H), 2.19 (s, 3H), 2.54 (s, 3H), 7.20−7.28 (m, 10); ^{13}C NMR δ 17.5, 18.8, 31.3, 48.7, 126.6, 127.9, 128.2, 140.6, 147.4, 147.9, 161.4; EI MS 293 (M^+); HRMS *m/z* calcd for $C_{19}H_{19}NS$ 293.1238, found 293.1234.

3-(1,1-Diphenylethyl)quinoline (16): mp 126−128 °C (C_6H_6); ^1H NMR δ 2.31 (s, 3H), 7.14−7.18 (m, 4H), 7.20−7.37 (m, 6H), 7.46−7.55 (m, 2H), 7.96 (m, 2H), 8.09−8.12 (m, 1H), 8.80 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ 30.4, 51.5, 126.7, 126.9, 127.9, 128.1, 128.2, 128.3, 128.9, 129.1, 129.4, 129.5, 133.4, 134.6, 152.5; EI MS 309 (M^+); HRMS *m/z* calcd for $C_{23}H_{19}N$ 309.1517, found 309.1514.

3-(1,1-Diphenylethyl)isoquinoline (17): mp 117−120 °C (C_6H_6); ^1H NMR δ 2.39 (s, 3H), 7.19−7.36 (m, 10H), 7.39 (s, 1H), 7.54−7.68 (m, 3H), 7.97 (d, J = 8.1 Hz, 1H), 9.32 (s, 1H); ^{13}C NMR δ 29.7, 55.0, 119.4, 126.4, 127.1, 127.2, 127.5, 128.2, 128.3, 128.6, 129.1, 130.5, 136.2, 148.6, 152.1, 161.2; EI MS 309 (M^+); HRMS *m/z* calcd for $C_{23}H_{19}N$ 309.1517, found 309.1522.

Reaction of 1-Acetylisoquinoline (9). A 0.2 g (1.2 mmol) portion of compound **9** was reacted with TfOH (10 mL) and C_6H_6 (2 mL) at 50 °C for 24 h. As described in the general procedure, the product mixture was worked up, and the products were isolated by column chromatography (9:1 hexanes/ether).

1-(1,1-Diphenylethyl)isoquinoline (18): 0.004 g (0.014 mmol, 1% yield); mp 134−137 °C (C_6H_6); ^1H NMR δ 2.32, 7.10−7.38 (m, 11H), 7.47 (m, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 5.7 Hz, 1H), 8.55 (d, J = 5.7 Hz, 1H); ^{13}C NMR δ 34.1, 57.1, 120.7, 125.9, 126.2, 127.5, 127.7, 128.2, 128.9, 129.0, 129.1, 137.5, 141.1, 147.5, 165.2; EI MS 309 (M^+).

1-(1-Phenylethenyl)isoquinoline (19): 0.158 g (0.69 mmol, 57% yield); mp 41−45 °C (C_6H_6); ^1H NMR δ 5.53 (d, J = 0.6 Hz, 1H), 6.13 (d, J = 0.6 Hz, 1H), 7.25−7.33 (m, 6H), 7.47 (m, 1H), 7.66 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 5.7 Hz, 1H); ^{13}C NMR δ 118.0, 120.5, 126.2, 126.9, 127.1, 127.4, 127.7, 128.2, 128.7, 129.0, 130.3, 136.8, 142.5; EI MS 231 (M^+); HRMS *m/z* calcd for $C_{17}H_{12}N$ (M − H) 230.0970, found 230.0961.

4-(1,1-Diphenylpropyl)pyridine (20): mp 41−44 °C ($CHCl_3$); ^1H NMR δ 0.98 (t, J = 7.2 Hz, 3H), 2.83 (q, J = 7.2 Hz, 2H), 7.30−7.62 (m, 12H), 8.7 (m, 2H); ^{13}C NMR δ 10.1, 32.0, 58.8, 124.4, 126.2, 128.0, 129.1, 145.5, 149.3, 156.4; EI MS 273 (M^+); HRMS *m/z* calcd for $C_{20}H_{19}N$ 273.1392, found 273.1506.

Reaction of 2-acetylpyrazine (28). A 0.305 g (2.5 mmol) portion of compound **28** was reacted with TfOH (7 mL) and C_6H_6 (1 mL) at 50 °C for 24 h. As described in the general procedure, the product mixture was worked up and the products were isolated by column chromatography (3:1 hexanes/ether).[20]

2-(1,1-Diphenylethyl)pyrazine (29): 0.0623 g (0.24 mmol, 10% yield); ^1H NMR δ 2.25 (s, 3H), 7.09−7.14 (m, 4H), 7.24−7.34 (m, 6H), 8.0.36 (d, J = 1.5 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.58 (dd, J = 1.5, 2.4 Hz, 1H); ^{13}C NMR δ 29.1, 53.4, 126.5, 128.2, 128.4, 141.7, 143.4, 145.1, 147.0, 162.7; EI MS 260 (M^+); HRMS *m/z* calcd for $C_{18}H_{16}N_2$ 260.1313, found 260.1323.

2-Acetyl-6-phenylpyrazine (30): 0.0616 g (0.311 mmol, 12% yield); mp 158−159 °C ($CHCl_3$); ^1H NMR δ 2.73 (s, 3H), 7.52−7.55 (m, 3H), 8.07 (m, 2H), 9.05 (d, J = 1.5 Hz, 1H), 9.25 (d, J = 1.5 Hz, 1H); ^{13}C NMR δ 25.9, 127.4, 129.2, 130.8, 135.4, 140.5, 142.9, 145.6, 155.1, 199.1; EI MS 198 (M^+); HRMS *m/z* calcd for $C_{12}H_{10}N_2O$ 198.0793, found 198.0793.

2-(1,1-Diphenylethyl)-6-phenylpyrazine (31): 0.0224 g (0.07 mmol, 3% yield); ^1H NMR δ 2.27 (s, 3H); 7.14−7.17 (m, 4H), 7.25−7.34 (m, 7H), 7.47−7.50 (m, 2H), 7.99−8.02 (m, 2H), 8.38 (d, J = 1.5 Hz, 1H), 9.03 (d, J = 1.5 Hz, 1H); ^{13}C NMR δ 29.3, 46.3, 126.7, 127.0, 128.5, 128.7, 129.2, 129.4, 129.9, 131.3, 136.5, 140.7, 144.4, 147.4; EI MS 336 (M^+); HRMS *m/z* calcd for $C_{24}H_{19}N_2$ (M − H) 335.1548, found 335.1544.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **10**−**20** and **29**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) By gas chromatography, the yields of the products were considerably higher than that measured for the isolated yields. Due to poorly resolved fractions in the chromatography, some product was lost.