Synthesis of Bis(2-arylquinolin-4-yl)amines by Lithium Bis(trimethylsilyl)amide-Mediated Cyclization of Ketimines Derived from 2-(Trifluoromethyl)anilines and Aryl Methyl Ketones

Lucjan Strekowski,* Lubomir Janda,[1] and Hyeran Lee

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

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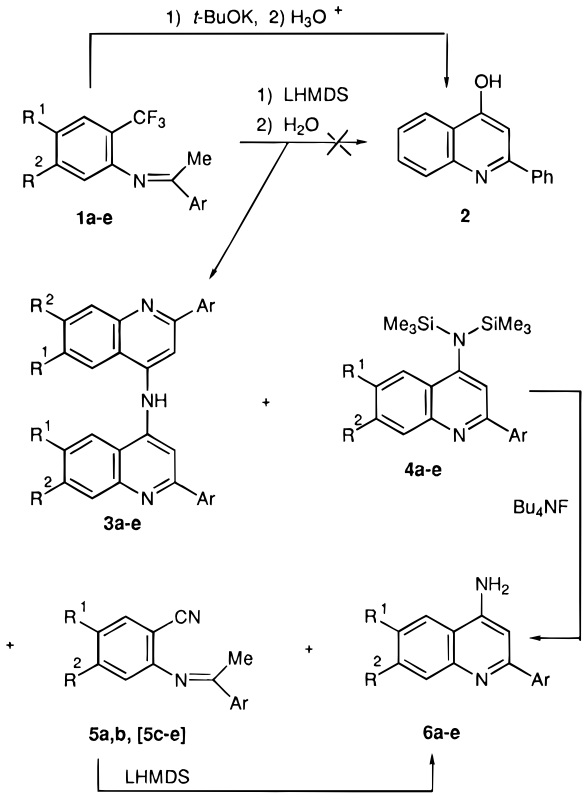
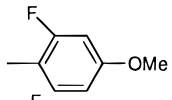
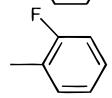
In 1990, we reported a novel base-mediated cyclization of *o*-(trifluoromethyl)-substituted ketimines such as **1** (Scheme 1) to quinolines.[2] Subsequently, this and related chemistry have been elaborated into a practical tool for the construction of various substituted and fused quinolines, quinazolines, and other heterocyclic and nonheterocyclic systems.[3] In particular, the cyclization of **1** in the presence of *t*-BuOK followed by acid hydrolysis of the resultant 4-*tert*-butoxyquinoline[4] yields a 4-hydroxyquinoline such as **2**. Unfortunately, in the original paper,[2] it was also stated erroneously that the same 4-hydroxyquinoline **2** was produced in the reaction of **1a** with lithium bis(trimethylsilyl)amide (LHMDS) followed by aqueous workup. This paper is a correction to the previously published paper.[5]

The treatment of ketimines **1a**−**e** with LHMDS (3.5 equiv) gave the corresponding bis(quinolyl)amines **3a**−**e** and silylated quinolinamines **4a**−**e** as the major and minor products, respectively. Compounds **3** and **4** were easily separated by flash chromatography. A detailed chromatographic separation of the mixtures from **1a,b** also revealed the presence of known cyano-substituted ketimines[6] **5a,b** and trace amounts of quinolinamines[6] **6a,b** as additional minor products with a total mass balance for **3**−**6** of at least 95% in each case. These results were confirmed by GC−MS analyses of crude mixtures from **1a,b**. In a similar way, the GC−MS analysis of the crude mixtures from **1c**−**e** showed the presence of varying amounts of two additional minor products (not isolated in pure form by conventional chromatography) with a molecular ion peak and fragmentation pattern fully consistent with the respective structures **5c**−**e** and **6c**−**e**.

All bis(quinolyl)amines **3a**−**e** gave a molecular ion peak as the base peak in their mass spectra. The silyl derivatives **4a**−**e** are also relatively stable under electron impact conditions. An intense molecular ion peak was observed, and the loss of methyl from the molecular ion accounts for the most abundant fragment ion for **4a**−**e**.

Scheme 1



3-6	R^1	R^2	Ar
a	H	H	Ph
b	H	H	
c	H	CF_3	Ph
d	H	CF_3	
e	F	H	

As expected, compounds **4** were easily and efficiently desilylated by treatment with tetrabutylammonium fluoride to give quinolin-4-amines **6**. The formation of known quinolines[6] **6a,b** under these conditions served as an additional confirmation of the structure of **4a,b**. The isolated ketimines **5a,b** were cyclized to **6a,b** by using a previously published procedure.[6]

The highest yields of bis(quinolyl)amines **3** (48−73%) were obtained with 3.0−3.5 equiv of LHMDS. The use of 20 equiv of the reagent resulted in greatly diminished yields of both **3** and ketimines **5**, and *N*,*N*-bis(trimethylsilyl)quinolin-4-amines **4** were the major products (58−62%). To determine whether or not products **4**−**6** are precursors to bis(quinolyl)amines **3**, several cross experiments were conducted under standard conditions (3.5 equiv of LHMDS). The efficiency of cyclization of **1a** to **3a** was increased from 48% to 65% for the reaction conducted in the presence of 1 equiv of quinolinamine **6a**. As expected, a similarly increased yield of **3a** was obtained in the presence of 1 equiv of ketimine **5a** because **5a** is easily cyclized to **6a** under strongly basic conditions.[6] Another experiment was conducted with a

* To whom correspondence should be addressed. Tel.: (404) 651-0999. Fax: (404) 651-1416. E-mail: Lucjan@gsu.edu.
(1) Current address: Aldrich Chemical Co., Inc., Milwaukee, WI 53233.

(2) Strekowski, L.; Wydra, R. L; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. *J. Org. Chem.* **1990**, *55*, 4777.
(3) For a review, see: Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proc. Int.* **1996**, *28*, 289.
(4) (a) Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. *J. Heterocycl. Chem.* **1992**, *29*, 1753. (b) Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R. L.; Harden, D.B.; Lipowska, M.; Cegla, M. T. *J. Org. Chem.* **1992**, *57*, 196.
(5) It appears that, due to mislabeling, a sample of **2** was found to be identical with itself.
(6) Strekowski, L.; Kong, S.-B.; Cegla, M. T.; Harden, D. B. *Heterocycles* **1989**, *29*, 539.

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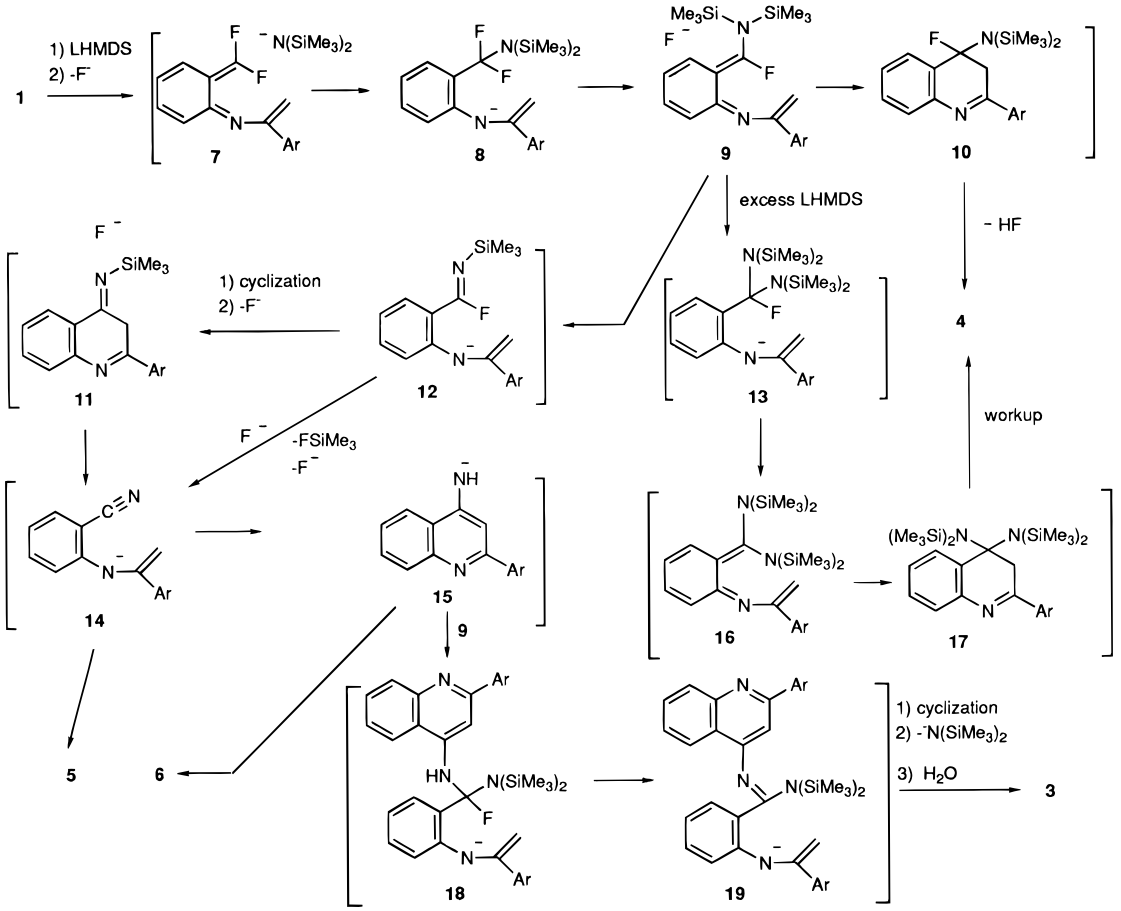
Scheme 2



mixture of ketimine **1a** and quinolinamine **6b** (1 equiv each). Preparative chromatography gave an inseparable mixture of two bis(quinolyl)amines. The mass spectrum of this mixture showed a strong molecular ion peak for **3a** at *m/z* 423 and a more intense peak at *m/z* 429, which may correspond to the molecular ion of bis-(quinolin-4-yl)amine substituted with phenyl and 2-thienyl groups at the 2 and 2′ positions (not shown). Ketimine **1a** was also cyclized in the presence of a silyl derivative **4b** (1 equiv). Preparative chromatography gave a mixture of **4a** and **4b** and pure (by ^{1}H NMR standard) compounds **3a**, **5a**, and **6a**. NMR integration of the fraction containing **4a** and **4b** revealed that **4b** was recovered in a 90% yield. The relative stability of silylamines **4** under the reaction conditions was confirmed by conducting the reaction of **1b** under standard conditions (45 min), quenching half of the mixture, and then quenching the second half after 1.5 h, which resulted in only a slightly decreased yield of **4b**. These results show that (i) quinolinamines **6** are precursors to bis-(quinolyl)amines **3** and (ii) the major pathway to **6** involves cyclization of intermediate ketimines **5** but not desilylation of (trimethylsilyl)amines **4**.

A unified mechanism for **3**−**6**, which is consistent with the above observations, is suggested in Scheme 2. The initial transformations **1** → **7** → **8** → **9** are well understood for a variety of strong bases/nucleophiles.[2−4] While the key intermediate product **9** can, in principle, undergo electrocyclization to **10**, a possible direct precursor to a silylamine **4**, this electrocyclization is apparently slower than the competing nucleophilic addition of bis(trimethylsilyl)amide anion with **9** to generate **13**. The subsequent pathway **13** → **16** → **17** → **4** is straightforward.[7] The suggested nucleophile addition to **9** is consistent with the experimental finding that the yield of a silylamine **4** increases with increasing concentration of bis(trimethylsilyl)amide anion (up to 20 equiv).

On the other hand, the bis(quinolyl)amine **3** is formed efficiently in the presence of 3.5 equiv of the lithium reagent,[8] and under optimized conditions the reagent is added in portions to the mixture resulting in a low concentration of the amide anion throughout the reaction course. It is suggested that under these conditions the fluoride ion-assisted desilylation of **9** competes effectively with the nucleophile addition, the driving force being the formation of the aromatic structure **12**. Anion **14** of the observed product **5** can be formed in two pathways: (i) fluoride ion-mediated desilylation of **12** and elimination of the remaining fluoride or (ii) intramolecular cyclization of **12** (intramolecular addition of azaallyl anion to fluoro imine) followed by fluoride-assisted desilylation and ring opening of the resultant intermediate product **11**. The apparent driving force of both pathways is the formation of a thermodynamically stable cyano group.[9] The known cyclization[6] of **14** is followed by nucleophilic addition of

(7) See refs 2 and 4b for close analogs of **17**.

(8) The suggested pathway from **1** to a lithium derivative of **3** requires 3 equiv of lithium bis(trimethylsilyl)amide.

(9) The treatment of 2- or 4-(trifluoromethyl)aniline with sodium amide in liquid ammonia gives the respective 2- or 4-aminobenzonitrile in a low yield: Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197. We have found (unpublished results) that 2-aminobenzonitrile is produced in a 20% yield by the reaction of 2-(trifluoromethyl)aniline with 3.1−3.5 equiv of lithium bis(trimethylsilyl)amide under the general conditions of this paper. The use of an excess of the lithium reagent (20 equiv) gave only traces of 2-aminobenzonitrile, which is completely analogous to the reactions of **1**.

the resultant quinolylamide anion **15** with the key intermediate product **9** to give **18**. The remaining steps **18** → **19** → **3** are self-explanatory.

In summary, we have shown that the reaction of ketimines **1** with LHMDS gives symmetrical bis(quinolin-4-yl)amines **3** in good yields. The proposed mechanism is fully consistent with the experimental findings including all isolated minor products. The method is not practical for the synthesis of unsymmetrically substituted amines **3** due to the formation of two amines **3** that are difficult to separate.

Experimental Section

Melting points (Pyrex capillary) are not corrected. Proton and ^{13}C NMR spectra were recorded at 400 and 67.8 MHz, respectively. Mass spectra were determined at 70 eV.

Ketimines 1a−f. Synthesis of **1a**,[10] **1b**,[10] **1c**,[4a] and **1e**[11] has been reported previously. Ketimine **1d** was obtained in a similar fashion by condensation of 2,5-bis(trifluoromethyl)aniline with 2′-fluoro-4′-methoxyacetophenone.

***N*-[1-(2-Fluoro-4-methoxyphenyl)ethylidene]-2,5-bis(trifluoromethyl)aniline (1d):** yield 65%; bp 158−159 °C/3.8 mmHg; mp 58−59 °C; ^1H NMR ($CDCl_3$) δ 2.25 (d, J_{HF} = 3.6 Hz, 3 H), 3.86 (s, 3 H), 6.66 (d, J_{HF} = 13.6 Hz, 1 H), 6.79 (d, J = 8.6 Hz, 1 H), 7.07 (s, 1 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.89 (t, J_{HF} = J_{HH} = 8.6 Hz, 1 H); MS *m*/*z* 364 (100), 379 (40, M^+). Anal. Calcd for $C_{17}H_{12}F_7NO$: C, 53.83; H, 3.19; N, 3.69. Found: C, 53.93; H, 3.18; N, 3.65.

Reaction of Ketimines 1a−e with Lithium Bis(trimethylsilyl)amide: Method A. A solution of **1** (1.0 mmol) in anhydrous THF (10 mL) was stirred under a nitrogen atmosphere at 23 °C and treated dropwise with a solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 2.0 mL, 2.0 mmol). After 20 min, the mixture was treated with another portion of the lithium reagent (1.5 mL, 1.5 mmol) and stirred at 23 °C for an additional 25 min. A dark-red mixture was quenched with water (90 μL, 5 mmol), filtered, and concentrated on a rotary evaporator, leaving a light-orange residue. Silica gel chromatography on a chromatotron gave, in order of elution, **4**, **5** (hexanes/Et_3N, 9:1), **3** (hexanes/Et_3N/EtOH, 6:2:2), and trace amounts (<3%) of **6** (hexanes/Et_3N/EtOH, 4:4:2). Products **4** and **5** were crystallized from hexanes and **3** from a mixture of EtOH, THF, and hexanes.

Bis(2-phenylquinolin-4-yl)amine (3a): yield 48%; mp 259−260 °C; ^1H NMR (DMSO-d_6) δ 7.44 (m + s, 8 H), 7.56 (t, J = 7.8 Hz, 2 H), 7.65 (br s, exchangeable with D_2O, 1 H), 7.78 (t, J = 7.8 Hz, 2 H), 8.07 (m, 6 H), 8.32 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 107.1, 121.2, 123.3, 125.7, 127.2, 129.0, 129.7, 129.8, 130.4, 139.1, 148.2, 149.3, 156.8; MS *m*/*z* 320 (40), 422 (70), 423 (100, M^+). Anal. Calcd for $C_{30}H_{21}N_3$: C, 85.07; H, 4.99; N, 9.92. Found: C, 84.84; H, 5.02; N, 9.86.

Bis[2-(2-thienyl)quinolin-4-yl]amine (3b): yield 73%; mp 265−267 °C; ^1H NMR (DMSO-d_6) δ 7.09 (dd, J = 5.0, 3.8 Hz, 2 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.64 (m + s, 7 H), 7.76 (t, J = 8.0 Hz, 2 H), 7.98 (d, J = 8.0 Hz, 2 H), 8.28 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 105.7, 121.1, 123.0, 125.3, 126.3, 128.4, 129.0, 129.2, 130.3, 145.0, 147.5, 148.9, 152.3; MS *m*/*z* 326 (20), 434 (30), 435 (100, M^+). Anal. Calcd for $C_{26}H_{17}N_3S_2$: C, 71.69; H, 3.94; N, 9.64. Found: C, 71.52; H, 3.92; N, 9.59.

Bis[2-phenyl-7-(trifluoromethyl)quinolin-4-yl]amine (3c): yield 65%; mp 236−238 °C; ^1H NMR (DMSO-d_6) δ 7.47 (m, 7 H), 7.84 (d, J = 8 Hz, 2 H), 7.90 (s, 2 H), 8.14 (m, 4 H), 8.41 (s, 2 H), 8.58 (d, J = 8 Hz, 2 H); MS *m*/*z* 456 (50), 558 (70), 559 (100, M^+). Anal. Calcd for $C_{32}H_{19}F_6N_3$: C, 68.67; H, 3.42; N, 7.51. Found: C, 68.85; H, 3.50; N, 7.51.

Bis[2-(2-fluoro-4-methoxyphenyl)-7-(trifluoromethyl)quinolin-4-yl]amine (3d): yield 69%; mp 158−160 °C; ^1H NMR (DMSO-d_6) δ 3.82 (s, 6 H), 6.92 (m, 5 H), 7.67 (s, 2 H), 7.84 (m, 2 H), 8.08 (m, 2 H), 8.36 (m, 2 H), 8.57 (m, 2 H); MS *m*/*z* 504 (30), 654 (50), 655 (100, M^+). Anal. Calcd for $C_{34}H_{21}F_8N_3O_2$: C, 62.29; H, 3.23; N, 6.41. Found: C, 62.21; H, 3.46; N, 6.40.

Bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine (3e): yield 57%; mp 275−277 °C; ^1H NMR (DMSO-d_6) δ 7.26 (t, J = 8 Hz, 2 H), 7.30 (br s, exchangeable with D_2O, 1 H), 7.32 (t, J = 8 Hz, 2 H), 7.48 (m, 2 H), 7.61 (s, 2 H), 7.73 (m, 2 H), 8.02 (m, 2 H), 8.16 (m, 4 H); MS *m*/*z* 374 (40), 494 (50), 495 (100, M^+). Anal. Calcd for $C_{30}H_{17}F_4N_3$: C, 72.72; H, 3.46; N, 8.48. Found: C, 72.53; H, 3.48; N, 8.42.

***N*,*N*-Bis(trimethylsilyl)-2-phenylquinolin-4-amine (4a):** yield 26%; mp 87−89 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 18 H), 7.43 (s, 1 H), 7.50 (m, 5 H), 7.67 (m, 1 H), 8.14 (m, 3 H); MS *m*/*z* 349 (100), 364 (25, M^+). Anal. Calcd for $C_{21}H_{28}N_2Si_2$: C, 69.17; H, 7.74; N, 7.68. Found: C, 69.21; H, 7.71; N, 7.61.

***N*,*N*-Bis(trimethylsilyl)-2-(2-thienyl)quinolin-4-amine (4b):** yield 7%; mp 105−106 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 18 H), 7.16 (dd, J = 5.2, 3.6 Hz, 1 H), 7.35 (s, 1 H), 7.44 (t, J = 8 Hz, 1 H), 7.47 (d, J = 5.2 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.69 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 8 Hz, 1 H), 8.06 (d, J = 8 Hz, 1 H); MS *m*/*z* 355 (100), 370 (30, M^+). Anal. Calcd for $C_{19}H_{26}N_2SSi_2$: C, 61.56; H, 7.07; N, 7.56. Found: C, 61.62; H, 7.07; N, 7.53.

***N*,*N*-Bis(trimethylsilyl)-2-phenyl-7-(trifluoromethyl)quinolin-4-amine (4c):** yield 21%; mp 101−103 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 18 H), 7.52 (s, 1 H), 7.54 (m, 3 H), 7.66 (d, J = 8 Hz, 1 H), 8.15 (m, 2 H), 8.23 (d, J = 8 Hz, 1 H), 8.45 (br s, 1 H); MS *m*/*z* 417 (100), 432 (20, M^+). Anal. Calcd for $C_{22}H_{27}F_3N_2Si_2$: C, 61.07; H, 6.29; N, 6.47. Found: C, 61.00; H, 6.32; N, 6.41.

***N*,*N*-Bis(trimethylsilyl)-2-(2-fluoro-4-methoxyphenyl-7-(trifluoromethyl)quinolin-4-amine (4d):** yield 19%; mp 82−83 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 18 H), 3.88 (s, 3 H), 6.74 (d, J_{HF} = 13 Hz, 1 H), 6.89 (d, J = 8 Hz, 1 H), 7.56 (d, J_{HF} = 2.8 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 8.16 (t, J_{HH} = J_{HF} = 8 Hz, 1 H), 8.22 (d, J = 8 Hz, 1 H), 8.43 (br s, 1 H); MS *m*/*z* 465 (100), 480 (30, M^+). Anal. Calcd for $C_{23}H_{28}F_4N_2OSi_2$: C, 57.47; H, 5.87; N, 5.82. Found: C, 57.57; H, 5.83; N, 5.73.

***N*,*N*-Bis(trimethylsilyl)-6-fluoro-2-(2-fluorophenyl)quinolin-4-amine (4e):** yield 17%; mp 96−98 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 18 H), 7.18 (m, 1 H), 7.31 (m, 1 H), 7.44 (m, 2 H), 7.49 (d, J_{HF} = 2.8 Hz, 1 H), 7.73 (m, 1 H), 8.12 (m, 2 H); MS *m*/*z* 385 (100), 400 (45, M^+). Anal. Calcd for $C_{21}H_{26}F_2N_2Si_2$: C, 62.95; H, 6.54; N, 6.99. Found: C, 62.67; H, 6.82; N, 6.70.

2-[(1-Phenylethylidene)amino]benzonitrile (5a): yield 22%; mp 67−68 °C (lit.[6] mp 68−69 °C).

2-[[1-(2-Thienyl)ethylidene]amino]benzonitrile (5b): yield 15%; mp 86−87 °C (lit.[6] mp 85−87 °C).

Reaction of Ketimines 1a,b with Lithium Bis(trimethylsilyl)amide: Method B. The lithium reagent (20 mmol) was added in one portion to a solution of **1** (1.0 mmol) in THF (5 mL), and the resultant mixture was stirred at 23 °C for 45 min and then worked up as described in method A to give **3a** (19%), **4a** (58%), **5a** (10%); **3b** (16%), **4b** (62%), **5b** (7%).

Desilylation of *N*,*N*-Bis(trimethylsilyl)quinolin-4-amines 4a−e. A solution of a silyl derivative **4a**−**e** (0.2 mmol) and tetrabutylammonium fluoride hydrate (0.25 g, 0.8 mmol) in THF (10 mL) was stirred at 23 °C under a nitrogen atmosphere for 2 h and then concentrated on a rotary evaporator. Products **6a**−**e** were isolated by silica gel chromatography on a chromatotron eluting with hexanes/Et_3N/EtOH (4:2:2) and then crystallized from 95% EtOH/hexanes.

2-Phenylquinolin-4-amine (6a): yield 94%; mp 163−164 °C (lit.[6] mp 163−165 °C).

2-(2-Thienyl)quinolin-4-amine (6b): yield 90%; mp 163−165 °C (lit.[6] mp 163−165 °C).

2-Phenyl-7-(trifluoromethyl)quinolin-4-amine (6c): yield 92%; mp 130−132 °C; ^1H NMR ($CDCl_3$) δ 4.80 (br s, exchangeable with D_2O, 2 H), 7.17 (s, 1 H), 7.49 (m, 3 H), 7.61 (d, J = 8 Hz, 1 H), 7.87 (d, J = 8 Hz, 1 H), 8.09 (m, 2 H), 8.40 (br s, 1 H); MS *m*/*z* 287 (80), 288 (100, M^+). Anal. Calcd for $C_{16}H_{11}F_3N_2$: C, 66.65; H, 3.84; N, 9.72. Found: C, 66.32; H, 4.08; N, 9.58.

2-(2-Fluoro-4-methoxyphenyl)-7-(trifluoromethyl)quinolin-4-amine (6d): yield 92%; mp 110−111 °C; ^1H NMR ($CDCl_3$/DMSO-d_6, 1:1) δ 3.87 (s, 3 H), 5.61 (br s, exchangeable with D_2O, 2 H), 6.71 (d, J_{HF} = 16 Hz, 1 H), 6.86 (d, J = 8 Hz, 1 H), 7.19 (d, J_{HF} = 2 Hz, 1 H), 7.57 (d, J = 8 Hz, 1 H), 8.06 (m, 2 H), 8.31 (s, 1 H); MS *m*/*z* 273 (15), 336 (100, M^+). Anal. Calcd for

(10) Strekowski, L.; Mokrosz, J. L.; Honkan, V. A.; Czarny, A.; Cegla, M. T.; Wydra, R. L.; Patterson, S. E.; Schinazi, R. F. *J. Med. Chem.* **1991**, *34*, 1739.

(11) Strekowski, L.; Janda, L.; Patterson, S. E.; Nguyen, J. *Tetrahedron* **1996**, *52*, 3273.

$C_{17}H_{12}F_4N_2O \cdot 0.5H_2O$: C, 59.12; H, 3.79; N, 8.11. Found: C, 58.97; H, 3.83; N, 8.09.

6-Fluoro-2-(2-fluorophenyl)quinolin-4-amine (6e): yield 85%; mp 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 4.64 (br s, exchangeable with D_2O, 2 H), 7.13 (d, J_{HF} = 2 Hz, 1 H), 7.17 (m, 1 H), 7.29 (m, 1 H), 7.39 (m, 2 H), 7.45 (m, 1 H), 8.03 (m, 1 H), 8.08 m, 1 H); MS *m*/*z* 255 (50), 256 (100, M^+). Anal. Calcd for $C_{15}H_{10}F_2N_2$: C, 70.30; H, 3.93; N, 10.93. Found: C, 70.40; H, 3.97; N, 10.93.

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