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Amination by Lithium Alkylamide Reagents of Ketimines Derived from 2-(Trifluoromethyl)anilines and Methyl Halophenyl Ketones and Their Cyclization Products 2-(Halophenyl)quinolin-4-amines

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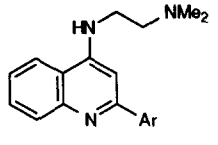
Abstract: The title ketimines containing a fluorine atom at position 2 of the phenyl group are efficiently cyclized under mild conditions to *N*-[2-(dimethylamino)ethyl]-2-(2-fluorophenyl)quinolin-4-amines by the reaction with a lithium reagent derived from *N,N*-dimethylethylenediamine. The facile regioselective displacement of C2-F in the presence of another fluorine atom at the phenyl group by the same reagent or *N*-lithio-*N'*-methylpiperazide at a higher temperature is explained in terms of a complex induced proximity effect (CIPE) process. The CIPE process is operative in amination of the 2-fluorophenyl ketimines by the more reactive piperazide reagent prior cyclization to quinolines. The 2-chlorophenyl derivatives are much less reactive in the CIPE assisted amination.

INTRODUCTION

Regiochemistry which takes place in close proximity to a substituent capable of complexing organolithium compounds has important synthetic ramifications. Directed *ortho* metalation of aromatic compounds, as reviewed by Snieckus[1] and Beak and Meyers[2] is mediated by a large number of functional groups and has received the most attention.[3] Other reports have described a complex-induced proximity effect (CIPE) in halogen-metal and metal-metal exchange reactions and additions to a carbon-carbon multiple bonds.[2] Only a few examples of displacement reactions have been explained in terms of a CIPE process.[2,4,5] In this paper we report for the first time that the nitrogen atom of 2-halophenyl ketimines and the quinoline ring nitrogen atom in 2-(2-halophenyl)quinolin-4-amines mediate regioselective nucleophilic displacement of the *ortho* halogen atom by reactions with lithium alkylamide reagents. The facility of the amination depends on the halogen and the amide reagent.

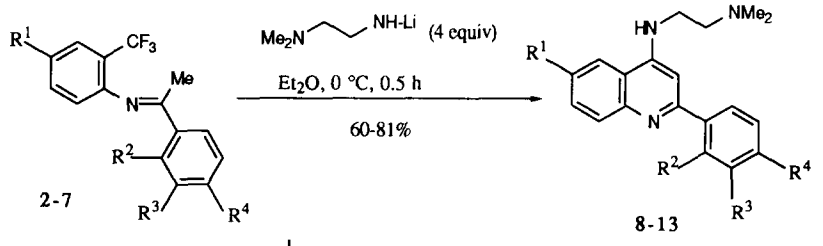


1: Ar = Ph, 2-naphthyl, heteroaryl

This study was initiated after it had been shown that quinoline derivatives **1** bind to nucleic acids. Intercalation with double-strand regions of viral RNA is apparently responsible for anti-HIV-1 activity of this class of compounds.[6] Several derivatives stabilize strongly and selectively a triple DNA structure containing consecutive AT sequences in the presence of duplex DNA of any sequence.[7] Such compounds are readily available[8] by lithium alkylamide mediated cyclization of ketimines derived from 2-(trifluromethyl)anilines and aryl methyl ketones. The cyclization reaction is shown in equation 1 by synthesis of new examples of quinolines **8-13** from the corresponding ketimines **2-7**. Since binding with DNA of a small molecule is, in general, enhanced by increasing positive charge on the molecule, it was of interest to synthesize additional derivatives substituted with an aliphatic amino group (normally protonated at pH 7). It was reasoned that the desired compounds could be obtained in an amination reaction of **8-13** and similarly substituted derivatives by lithium reagents derived from aliphatic diamines.

RESULTS AND DISCUSSION

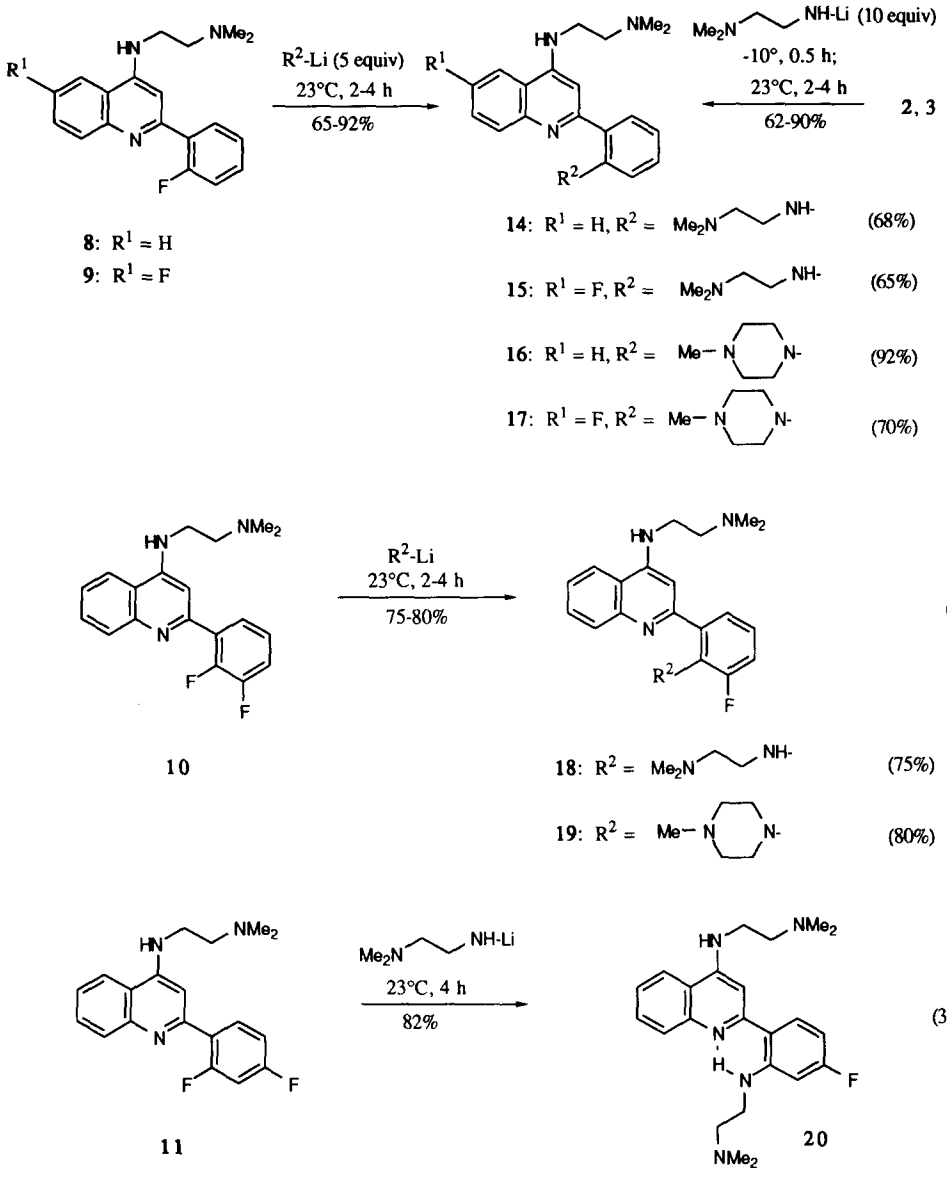
As can be seen from equation 1, the mild conditions for cyclization of ketimines 2-7 with *N*-lithio-2-(dimethylamino)ethylamide do not affect fluorine substituents at the quinoline and the phenyl group of the resultant products **8-13**. The treatment of isolated products **8, 9** (Scheme 1) with the same reagent or *N*-lithio-*N'*-methylpiperazide under conditions of a higher temperature and longer reaction time furnished the corresponding *ipso* 2-aminophenyl derivatives **14-17** as the sole regioisomers. With *N*-lithio-2-(dimethylamino)ethylamide the substrates were consumed in 4h at 23 °C and with the more reactive piperazide reagent the reaction was completed in 2h under similar temperature and concentration conditions. Neither reagent caused displacement of the 6-fluorine atom at the quinoline. In a one-pot synthesis of **14, 15** the ketimines **2, 3** were treated with an excess of *N*-lithio-2-(dimethylamino)ethylamide to give the respective product in a similar yield in comparison to that of the two-step procedure. The facility of nucleophilic displacement of the *ortho* fluorine atom is further indicated by the reactions of 2,3-difluorophenyl **10** (equation 2) and 2,4-difluorophenyl **11** (equation 3) derivatives, which yield the corresponding *ortho* amino products **18-20** with absolute regioselectivity.



(1)

2-13	R^1	R^2	R^3	R^4
2, 8	H	F	H	H
3, 9	F	F	H	H
4, 10	H	F	F	H
5, 11	H	F	H	F
6, 12	H	H	F	H
7, 13	H	H	H	F

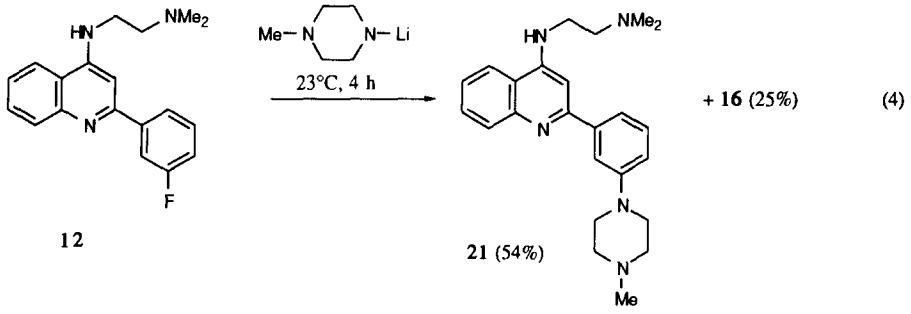
Scheme 1



Two important conclusions can be reached from these experiments. First, the *ortho*-fluoro substituted substrates **8**-**11** do not undergo lithiation adjacent to the fluorine atom. Such metalation would be followed by formation of a benzyne intermediate, which is not consistent with the observed regioselectivity of the amination. A second suggestion is that the regioselective substitution of the *ortho* fluorine atom is due to a CIPE process

mediated by complexation of the lithium amide reagent by the quinoline ring nitrogen atom. This amination apparently follows an S_NAr pathway facilitated by the electron withdrawing quinoline group, the nitrogen atom of which accommodates a negative charge in the intermediate σ adduct. The regioselective displacement of the more sterically hindered *ortho* fluorine rather than the sterically accessible *para* fluorine substituent in **11** is a strong argument for the CIPE process.

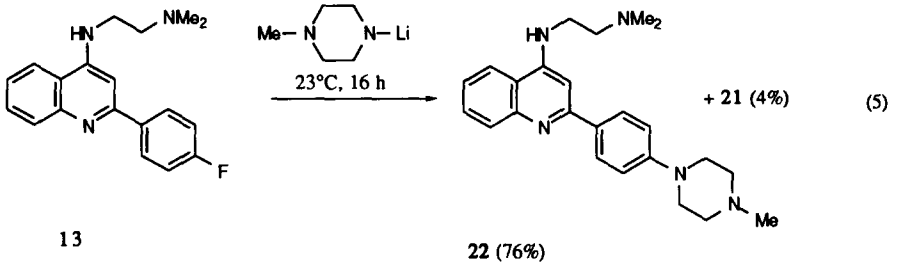
To be certain, an additional experiment with a *meta*-fluorophenyl derivative **12** was conducted (equation 4). Compound **12** cannot be substituted in an S_NAr process but, in principle, can undergo lithiation at positions 2 and 4 which are adjacent to the fluorine substituent at the phenyl moiety. It was reasoned that due to the presumed complexation of the lithium reagent by N1 of the quinoline the proximity effect should give rise to regioselective metalation at C2 of the phenyl. A subsequent generation of a 2,3-benzyne followed by an addition reaction with amine/amide anion should result in the formation of 2- and 3-amino regioisomers. On the other hand, a non-selective metalation of **12** would give rise to 2,3- and 3,4-benzynes resulting in the formation of a mixture of 2-, 3-, and 4-aminophenyl derivatives.



12 **21** (54%)

As can be seen from equation 4, the reaction of **12** with *N*-lithio-*N'*-methylpiperazide yields a mixture of 2-amino **16** and 3-amino **21** regioisomers. A GC analysis of the crude mixture revealed the absence of a 4-amino isomer (*vide infra*). This result shows that compound **12** is metalated at position 2 of the phenyl. The 3-amino regioisomer **21** is the major product as expected for the addition reaction of amine/amide anion to the intermediate 2,3-benzyne substituted with an electron-withdrawing 2-quinolyl group.[9] The rather high proportion of the sterically crowded 2-regioisomer **16** may be due to a cage effect following metalation and then generation of benzyne. Metalation within the complex gives an amine which may be hydrogen bonded to N1 of the quinoline and may remain hydrogen bonded after the benzyne has been generated, thus increasing the probability of the addition to the adjacent C2 atom of the benzyne. Alternatively, the C-2 metalated intermediate product may form a new complex with a lithium amide reagent with the involvement of the N1 atom of the quinoline.

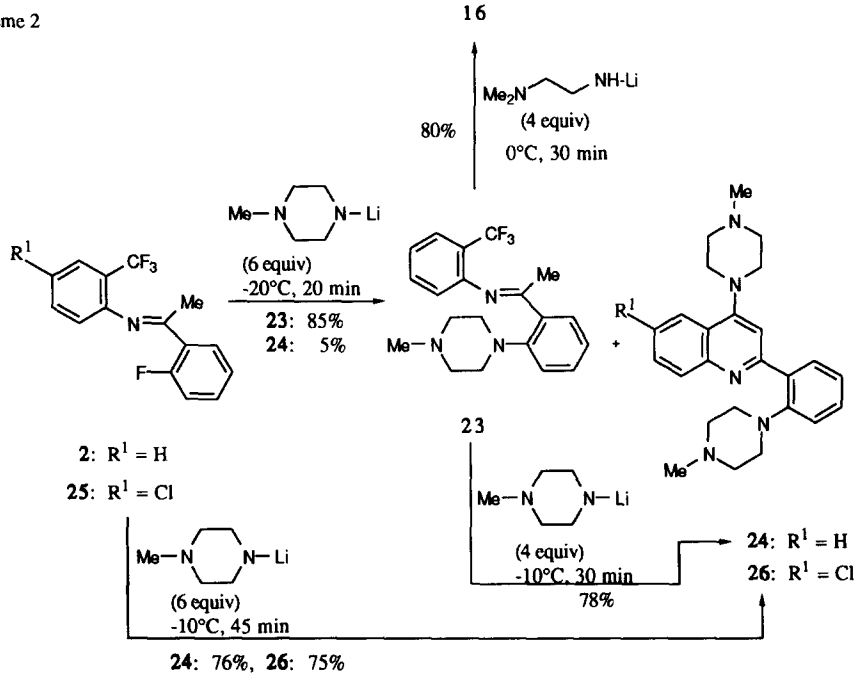
In order to obtain an additional insight into the discussed aminations, the reaction of 4-fluorophenyl derivative **13** with the piperazide reagent was conducted (equation 5). The formation of the major *ipso* product **22** and a minor *cine* isomer **21** is fully expected for the addition of amine/amide anion to an intermediate 3,4-benzyne substituted with an electron withdrawing 2-quinolyl group.[9] In this case, however, the rather large ratio of **22** to **21** may be due, in part, to a competing S_NAr pathway. An interesting observation is that the reaction of **12** (equation 4) is completed faster than the amination of **13**. The result indirectly supports the CIPE



assisted amination of **12**. Overall, the facility of amination of closely related monofluorophenyl derivatives with *N'*-lithio-*N*-methylpiperazide decreases in the following order: **8** (*o*-F) > **12** (*m*-F) > **13** (*p*-F).

In contrast to the cyclization reaction of 2-fluorophenyl ketimines with *N*-lithio-2(dimethylamino)ethylamide (equation 1), a similar treatment of the 2-fluorophenyl ketimines with *N'*-lithio-*N'*-methylpiperazide did not produce the expected 2-(2-fluorophenyl)-4-(*N*-methylpiperazino)quinolines under a variety of experimental conditions (Scheme 2). In particular, the substrate **2** was consumed quickly under extremely mild conditions to give a 2-(*N*-methylpiperazino)phenyl ketimine **23** and a quinoline **24** as a major and minor product, respectively. The yield of **24** increased and the yield of **23** decreased with increasing temperature and/or reaction time. Compound **24** was the only low molecular weight product for the reaction of **2** conducted under

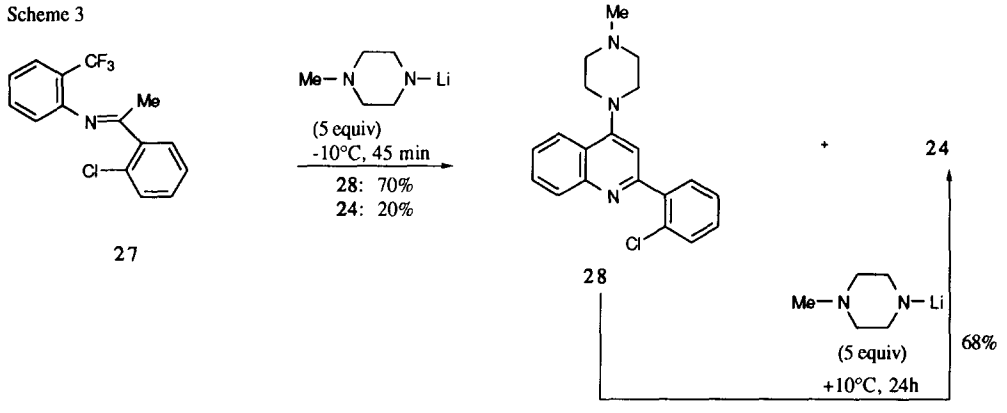
Scheme 2



mild conditions similar to those of a standard cyclization of ketimines with the piperazide reagent. Moreover, treatment of ketimine **23** with *N*-lithio-2-(dimethylamino)ethylamide or *N*-lithio-*N'*-methylpiperazide gave the respective cyclization products **16** and **24**. These results demonstrate that (1) nucleophilic displacement of fluoride from ketimine **2** by piperazide, apparently assisted by a CIPE process with the involvement of the ketimine nitrogen atom, is faster than cyclization of **2**, and (2) the ketimine **23** is an intermediate product in a major pathway of the transformation of **2** into **24**. The one-pot procedure was used to prepare quinoline **26** from the ketimine **25** (Scheme 2).[10]

A reaction of 2-chlorophenyl ketimine **27** with the piperazide reagent was also studied (Scheme 3). Two quinolines **28** and **24** as a major and minor product, respectively, were obtained under standard cyclization conditions at -10 °C, and a prolonged standing of the mixture at -10 °C did not affect the ratio of **28** to **24**. The *ipso* substitution of chloride in **28** was accomplished at a higher temperature. These results demonstrate that in comparison to the reaction of 2-fluorophenyl ketimine **2** with the lithium piperazide reagent, the amination of 2-chlorophenyl ketimine **27** competes less efficiently with cyclization of **27** to **28**.

Scheme 3



A final note is on structure determination which was obtained by comparative analysis of ^{1}H NMR spectra of the substrates and products. We have shown previously[8a,11] that ketimines derived from ring-substituted acetophenones and anilines under acid-catalyzed thermodynamic conditions are mixtures of *E* and *Z* diastereomers with the ratio of *E*/*Z*, in general, greater than 9:1. A long-range coupling constant $J_{H\text{-}F} = 4$ Hz between protons of the methyl group (δ 2.24 ± 0.04) and fluorine at position 2 of the phenyl group is observed in both ^{1}H NMR and ^{19}F NMR spectra of all *E* ketimines **2-5** and **25**. A doublet at δ 2.22 for Me in **2** gives way to a singlet at δ 2.24 for Me in the *ipso* substitution product **23**. Similarly, a doublet at δ 6.84 ± 0.02 ($J_{H\text{-}F} = 2.4$ Hz) for C3-H of the quinoline moiety of 2-(2-fluorophenyl)quinolines **8-11** is due to coupling of this proton with fluorine at position 2 of the phenyl group. The splitting of the C3-H signal is absent from ^{1}H NMR spectra of the corresponding *ipso* substitution products **14-20**. The N-H signal for 2-(dimethylamino)-ethylamino group at position 4 of quinolines **8-13, 16, 17, 19, 21,** and **22** is at δ 5.8 ± 0.2. In addition to a similar resonance for this 4-amino group in compounds **14, 15, 18,** and **20**, a second N-H signal is observed at δ 8.4 ± 0.6 for the second 2-(dimethylamino)ethylamino group at position 2 of the phenyl moiety. This distinct absorption is apparently due to intramolecular hydrogen bonding as exemplified for **20** (equation 3).

EXPERIMENTAL

General

All reactions with lithium reagents were conducted under nitrogen in glassware that had been stored in an oven at 120 °C. Ether was distilled from sodium benzophenone ketyl immediately before use. The progress of all reactions was monitored, and mass spectra of pure components were obtained on a GC-MS instrument equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column, and a mass selective detector operating at 70 eV. All yields are for analytically pure products. Melting points (Pyrex capillary) are not corrected. ^{1}H NMR spectra were taken in $CDCl_3$ solutions with TMS as an internal reference at 400 MHz, unless reported otherwise. Coupling constants smaller than 2 Hz are not reported.

Ketimines **2-7, 25, 27**

Acid catalyzed condensation of commercial anilines and ketones was conducted as described previously[6b] for the preparation of **7**. Ketimines were distilled on a Kugelrohr (100-150 °C /1 Torr). As shown by ^{1}H NMR all ketimines are mixtures of E and Z diastereomers, *E/Z* > 19:1. ^{1}H NMR spectra reported below are for *E* isomers. The stereochemistry was determined by NOE studies as described previously.[11]

N-[1-(2-Fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline (**2**). Yield 68%; ^{1}H NMR δ 2.22 (d, J_{H-F} = 4 Hz, 3 H), 6.83 (d, J = 8 Hz, 1 H), 7.1 - 7.3 (m, 3 H), 7.43 (m, 1 H), 7.52 (t, J = 8 Hz, 1 H), 7.67 (d, J = 8 = Hz, 1 H), 7.87 (t, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 266 (100), 281 (50, M^+). Anal. Calcd for $C_{15}H_{11}F_4N$: C, 64.05; H, 3.94; N, 4.98. Found: C, 64.32; H, 3.96; N, 4.92.

N-[1-(2-Fluorophenyl)ethylidene]-4-fluoro-2-(trifluoromethyl)aniline (**3**). Yield 70%; ^{1}H NMR δ 2.27 (d, J_{H-F} = 4 Hz, 3 H), 6.9 - 7.3 (m, 5 H), 7.45 (m, 1 H), 7.82 (m, 1 H); MS *m/z* (rel. int.) 284 (100), 299 (40, M^+). Anal. Calcd for $C_{15}H_{10}F_5N$: C, 60.21; H, 3.34; N, 4.68. Found: C, 60.10; H, 3.35; N, 4.60.

N-[1-(2,3-Difluorophenyl)ethylidene]-2-(trifluoromethyl)aniline (**4**). Yield 68%; ^{1}H NMR δ 2.23 (d, J_{H-F} = 4 Hz, 3 H), 6.82 (d, J = 8 Hz, 1 H), 7.1 - 7.3 (m, 3 H), 7.53 (t, J = 8 Hz, 1 H), 7.61 (t, J = 8 Hz, 1 H), 7.67 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 284 (100), 299 (40, M^+). Anal. Calcd for $C_{15}H_{10}F_5N$: C, 60.21; H, 3.34; N, 4.68. Found: C, 60.11; H, 3.40; N, 4.68.

N-[1-(2,4-Difluorophenyl)ethylidene]-2-(trifluoromethyl)aniline (**5**). Yield 71%; ^{1}H NMR δ 2.20 (d, J_{H-F} = 4 Hz, 3 H), 6.81 (d, J = 8 Hz, 1 H), 6.87 (m, 1 H), 6.97 (m, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.52 (t, J = 8 Hz, 1 H), 7.66 (d, J = 8 Hz, 1 H), 7.91 (m, 1 H); MS *m/z* (rel. int.) 284 (100), 299 (30, M^+). Anal. Calcd for $C_{15}H_{10}F_5N$: C, 60.21; H, 3.34; N, 4.68. Found: C, 60.22; H, 3.35; N, 4.68.

N-[1-(3-Fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline (**6**). Yield 90%; ^{1}H NMR (270 MHz) δ 2.19 (s, 3 H), 6.75 (d, J = 8 Hz, 1 H), 7.1 - 7.25 (m, 2 H), 7.42 (t, J = 8 Hz, 1 H), 7.50 (t, J = 8 Hz, 1 H), 7.65 - 7.75 (m, 3 H); MS *m/z* (rel. int.) 266 (100), 281 (40, M^+). Anal. Calcd for $C_{15}H_{11}F_4N$: C, 64.05; H, 3.94; N, 4.98. Found: C, 64.15; H, 3.95; N, 5.00.

N-[1-(2-Fluorophenyl)ethylidene]-4-chloro-2-(trifluoromethyl)aniline (**25**). Yield 60%; ^{1}H NMR (60 MHz) δ 2.24 (d, J_{H-F} = 4 Hz, 3 H), 6.78 (d, J = 8 Hz, 1 H), 6.9 - 8.1 (m, 6 H); MS *m/z* (rel. int.) 300 (100), 302 (30), 315 (30, M^+), 317 (10, M^+). Anal. Calcd for $C_{15}H_{10}ClF_4N$: C, 57.07; H, 3.19; N, 4.44. Found: C, 56.99; H, 3.21; N, 4.41.

N-[1-(2-Chlorophenyl)ethylidene]-2-(trifluoromethyl)aniline (**27**). Yield 85%; ^{1}H NMR (60 MHz) δ 2.20 (s, 3 H), 6.97 (t, J = 8 Hz, 1 H), 7.1 - 7.8 (m, 7 H); MS *m/z* (rel. int.) 282 (100), 284 (30), 297 (30, M^+), 299 (10, M^+). Anal. Calcd for $C_{15}H_{11}ClF_3N$: C, 60.52; H, 3.72; N, 4.70. Found: C, 60.40; H, 3.75; N, 4.68.

Reactions of Ketimines and Quinolines

All reactions with *N*-lithio-2-(dimethylamino)ethylamide or *N*-lithio-*N'*-methylpiperazide were conducted in ether as described previously[6b] for cyclization of ketimine **7** to quinoline **13**. A typical mixture (a final volume of 20 mL) contained a ketimine (6 mmol) or a quinoline (6 mmol) and a lithium amide reagent. The amount of the reagent and conditions are indicated at equations 1-5 and schemes 1-3 for each particular reaction. Workup, chromatography, and additional purification of aminoquinolines by crystallization of their hydrobromide salts from aqueous ethanol have been reported previously.[6b,8a]

N-[2-(Dimethylamino)ethyl]-2-(2-fluorophenyl)quinolin-4-amine (**8**). Yield 70%; an oil; ^{1}H NMR δ 2.32 (s, 6 H), 2.71 (t, J = 6 Hz, 2 H), 3.36 (m, 2 H), 5.93 (br s, exchangeable with D_2O, 1 H), 6.86 (d, J_{H-F} = 2.4 Hz, 1 H), 7.17 (m, 1 H), 7.28 (t, J = 8 Hz, 1 H), 7.39 (m, 1 H), 7.45 (t, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.81 (d, J = 8 Hz, 1 H), 8.02 (t, J = 8 Hz, 1 H), 8.06 (d, J = 8 Hz, 1 H); MS m/z (rel. int.) 58 (100), 309 (3, M^+). **8**•2HBr•H_2O: mp 242-243 °C. Anal. Calcd for $C_{19}H_{20}F_3N$•2HBr•H_2O: C, 46.64; H, 4.94; N, 8.58. Found: C, 46.92; H, 4.89; N, 8.50.

N-[2-(Dimethylamino)ethyl]-6-fluoro-2-(2-fluorophenyl)quinolin-4-amine (**9**). Yield 60%; an oil; ^{1}H NMR (60 MHz) δ 2.33 (s, 6 H), 2.72 (t, J = 6 Hz, 2 H), 3.35 (m, 2 H), 5.86 (br s, exchangeable with D_2O, 1 H), 6.86 (d, J_{H-F} = 2.4 Hz, 1 H), 7.0 - 8.6 (m, 7 H); MS m/z (rel. int.) 58 (100), 327 (3, M^+). **9**•2HBr•H_2O: mp 248-250 °C. Anal. Calcd for $C_{19}H_{19}F_2N_2$: C, 44.99; H, 4.57; N, 8.28. Found: C, 44.89; H, 4.60; N, 8.24.

N-[2-(Dimethylamino)ethyl]-2-(2,3-difluorophenyl)quinolin-4-amine (**10**). Yield 74%, an oil; ^{1}H NMR δ 2.34 (s, 6 H), 2.73 (t, J = 6 Hz, 2 H), 3.37 (m, 2 H), 6.02 (br s, exchangeable with D_2O, 1 H), 6.83 (d, J_{H-F} = 2.4 Hz, 1 H), 7.21 (m, 2 H), 7.47 (t, J = 8 Hz, 1 H), 7.66 (t, J = 8 Hz, 1 H), 7.77 (m, 1 H), 7.83 (d, J = 8 Hz, 1 H), 8.04 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 58 (100), 327 (5, M^+). HR-MS *m/z* calcd for $C_{19}H_{19}F_2N_3$ 327.1547, found *m/z* 327.1560.

N-[2-(Dimethylamino)ethyl]-2-(2,4-difluorophenyl)quinolin-4-amine (**11**). Yield 81%, an oil; ^{1}H NMR δ 2.32 (s, 6 H), 2.71 (t, J = 6 Hz, 2 H), 3.36 (m, 2 H), 5.95 (br s, exchangeable with D_2O, 1 H), 6.82 (d, J_{H-F} = 2.4 Hz, 1 H), 6.92 (m, 1 H), 7.02 (m, 1 H), 7.45 (t, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.81 (d, J = 8 Hz, 1 H), 8.03 (d, J = 8 Hz, 1 H), 8.06 (m, 1 H); MS *m/z* (rel. int.) 58 (100), 327 (5, M^+). HR-MS *m/z* calcd for $C_{19}H_{19}F_2N_3$ 327.1547, found *m/z* 327.1562.

N-[2-(Dimethylamino)ethyl]-2-(3-fluorophenyl)quinolin-4-amine (**12**). Yield 75%, an oil; ^{1}H NMR (60 MHz) δ 2.30 (s, 6 H), 2.63 (t, J = 6 Hz, 2 H), 3.30 (m, 2 H), 6.00 (br s, exchangeable with D_2O, 1 H), 6.80 (s, 1 H), 6.9 - 8.2 (m, 8 H); MS *m/z* (rel. int.) 58 (100), 309 (5, M^+). HR-MS *m/z* calcd for $C_{19}H_{20}FN_3$ 309.1641, found *m/z* 309.1630.

N-[2-(Dimethylamino)ethyl]-2-(4-fluorophenyl)quinolin-4-amine (**13**). Yield 80%; mp 134-136 °C (from toluene/hexanes), reported[6b] mp 134-136 °C.

N-[2-(Dimethylamino)ethyl]-2-[2-[[2-(dimethylamino)ethyl]amino]phenyl]quinolin-4-amine (**14**). Mp 150-151°C (from toluene/hexanes); ^{1}H NMR δ 2.31 (s, 6 H), 2.32 (s, 6 H), 2.65 (t, J = 6 Hz, 2 H), 2.71 (t, J = 6 Hz, 2 H), 3.31 (m, 2 H), 3.37 (m, 2 H), 5.84 (br s, exchangeable with D_2O, 1 H), 6.70 - 6.76 (m, 2 H), 6.77 (s, 1 H), 7.27 (m, 1 H), 7.41 (t, J = 8 Hz, 1 H), 7.62 (t, J = 8 Hz, 1 H), 7.66 (m, 1 H), 7.77 (d, J = 8 Hz, 1 H), 7.95 (d, J = 8 Hz, 1 H), 9.0 (br s, exchangeable with D_2O, 1 H); MS *m/z* (rel. int.) 319 (100), 320 (40), 377 (2, M^+). Anal. Calcd for $C_{23}H_{31}N_5$: C, 73.16; H, 8.27; N, 18.55. Found: C, 73.11; H, 8.33; N, 18.53.

N-[2-(Dimethylamino)ethyl]-2-[2-[[2-(dimethylamino)ethyl]amino]phenyl]-6-fluoroquinolin-4-amine (**15**). An oil; ^{1}H NMR δ 2.32 (s, 12 H), 2.63 (t, J = 6 Hz, 2 H), 2.71 (t, J = 6 Hz, 2 H), 3.30 (m, 2 H), 3.35 (m, 2 H), 5.67 (br s, exchangeable with D_2O, 1 H), 6.70 - 6.76 (m, 2 H), 6.78 (s, 1 H), 7.27 (m, 1 H), 7.35 - 7.43 (m, 2 H), 7.64 (m, 1 H), 7.95 (m, 1 H), 9.0 (br s, exchangeable with D_2O, 1 H); MS *m/z* (rel. int.) 337 (100), 395 (2, M^+). **15**•3HBr•H_2O: mp 238-240 °C. Anal. Calcd for $C_{23}H_{30}FN_5$•3HBr•H_2O: C, 40.96; H, 5.53; N, 10.38. Found: C, 41.11; H, 5.31; N, 10.25.

N-[2-(Dimethylamino)ethyl]-2-[2-(N-methylpiperazino)phenyl]quinolin-4-amine (**16**). An oil; ^{1}H NMR δ 2.29 (s, 3 H), 2.42 (s, 6 H), 2.44 (m, 4 H), 2.87 (t, J = 6 Hz, 2 H), 3.00 (m, 4 H), 3.56 (m, 2 H), 5.75 (br s, exchangeable with D_2O, 1 H), 7.13 (d, J = 8 Hz, 1 H), 7.18 (s, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.40 (t, J = 8 Hz, 1 H), 7.51 (t, J = 8 Hz, 1 H), 7.69 (t, J = 8 Hz, 1 H), 7.79 (d, J = 8 Hz, 1 H), 8.08 - 8.14 (m, 2 H); MS *m/z* (rel. int.) 58 (100), 319 (70), 389 (3, M^+). **16**•3HBr•1.5H_2O: mp 251-253 °C. Anal. Calcd for $C_{24}H_{31}N_5$•3HBr•1.5H_2O: C, 43.71; H, 5.65; N, 10.62. Found: C, 43.75; H, 5.68; N, 10.55.

N-[2-(Dimethylamino)ethyl]-6-fluoro-2-[2-(N-methylpiperazino)phenyl]quinolin-4-amine (**17**). An oil; ^{1}H NMR δ 2.23 (s, 3 H), 2.33 (s, 6 H), 2.36 (m, 4 H), 2.72 (t, J = 6 Hz, 2 H), 2.95 (m, 4 H), 3.37 (m, 2 H), 5.60 (br s, exchangeable with D_2O, 1 H), 7.06 (d, J = 8 Hz, 1 H), 7.13 (t, J = 8 Hz, 1 H), 7.23 (s, 1 H), 7.32 - 7.45 (m, 3 H), 7.67 (m, 1 H), 8.05 (m, 1 H); MS *m/z* (rel. int.) 58 (100), 337 (50), 407 (3, M^+). **17**•3HBr•2H_2O: mp 268-270 °C. Anal. Calcd for $C_{24}H_{30}FN_5$•3HBr•2H_2O: C, 41.99; H, 5.43; N, 10.20. Found: C, 41.93; H, 5.42; N, 10.17.

N-[2-(Dimethylamino)ethyl]-2-[2-[[2-(dimethylamino)ethyl]amino]-3-fluorophenyl]quinolin-4-amine (**18**). An oil; ^{1}H NMR δ 2.16 (s, 6 H), 2.32 (s, 6 H), 2.47 (t, J = 6 Hz, 2 H), 2.72 (t, J = 6 Hz, 2 H), 3.35 (m, 2 H), 3.40 (m, 2 H), 5.93 (br s, exchangeable with D_2O, 1 H), 6.70 (s, 1 H), 6.74 (m, 1 H), 7.02 (m, 1 H), 7.38 (d, J = 7 Hz, 1 H), 7.44 (t, J = 8 Hz, 1 H), 7.64 (t, J = 8 Hz, 1 H), 7.81 (d, J = 8 Hz, 1 H), 8.00 (d, J = 8 Hz, 1 H), 7.5 - 8.0 (br, exchangeable with D_2O); MS *m/z* (rel. int.) 337 (100), 395 (5, M^+). HR-MS *m/z* calcd for $C_{23}H_{30}FN_5$ 395.2485, found *m/z* 395.2499.

N-[2-(Dimethylamino)ethyl]-2-[3-fluoro-2-(N-methylpiperazino)phenyl]quinolin-4-amine (**19**). An oil; ^{1}H NMR δ 2.23 (s, 3 H), 2.33 (s, 6 H), 2.36 (m, 4 H), 2.73 (t, J = 6 Hz, 2 H), 2.95 (m, 4 H), 3.40 (m, 2 H), 5.86 (br s, exchangeable with D_2O, 1 H), 6.72 - 6.83 (m, 2 H), 7.13 (s, 1 H), 7.44 (t, J = 8 Hz, 1 H), 7.60 - 7.70 (m, 2 H), 7.82 (d, J = 8 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 58 (100), 337 (70), 407 (1, M^+). CI-MS (isobutane) 408 (100, M^+ +H). **19**•3HBr•2H_2O: mp 256-258 °C. Anal. Calcd for $C_{24}H_{30}FN_5$•3HBr•2H_2O: C, 41.99; H, 5.43; N, 10.20. Found: C, 42.10; H, 5.46; N, 10.15.

N-[2-(Dimethylamino)ethyl]-2-[2-[[2-(dimethylamino)ethyl]amino]-4-fluorophenyl]quinolin-4-amine (**20**). An oil; ^{1}H NMR (60 MHz) δ 2.23 (s, 6 H), 2.32 (s, 6 H), 2.4 - 2.75 (m, 4 H), 3.0 - 3.45 (m, 4 H), 5.8 (br s, exchangeable with D_2O, 1 H), 6.3 - 6.5 (m, 2 H), 6.72 (s, 1 H), 7.2 - 8.15 (m, 5 H), 9.6 (br s, exchangeable with D_2O, 1 H); MS *m/z* (rel. int.) 337 (100), 395 (2, M^+). **20**•3HBr•2H_2O: mp 208-210 °C. Anal. Calcd for $C_{23}H_{30}FN_5$•3HBr•2H_2O: C, 40.97; H, 5.53; N, 10.39. Found: C, 41.24; H, 5.52; N, 10.37.

N-[2-(Dimethylamino)ethyl]-2-[3-(N-methylpiperazino)phenyl]quinolin-4-amine (**21**). An oil; ^{1}H NMR δ 2.32 and 2.33 (2s, 9 H), 2.58 (t, J = 5 Hz, 4 H), 2.73 (t, 6 Hz, 2 H), 3.30 (t, J = 5 Hz, 4 H), 3.40 (m, 2 H), 5.97 (br s, exchangeable with D_2O, 1 H), 6.86 (s, 1 H), 7.00 (d, J = 8 Hz, 1 H), 7.36 (t, J = 8 Hz, 1 H), 7.43 (t, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 7.61 (t, J = 8 Hz, 1 H), 7.74 (br s, 1 H), 7.83 (d, J = 8 Hz, 1 H), 8.00 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 319 (100), 389 (8, M^+). **21**•3HBr•2.5H_2O: mp 240-241 °C. Anal. Calcd for $C_{24}H_{31}N_5$•3HBr•2.5H_2O: C, 42.55; H, 5.80; N, 10.34. Found: C, 42.51; H, 5.79; N, 10.30.

N-[2-(Dimethylamino)ethyl]-2-[4-(N-methylpiperazino)phenyl]quinolin-4-amine (**22**). Mp 132-133 °C (from toluene/hexanes); ^{1}H NMR δ 2.31 and 2.32 (2s, 9 H), 2.56 (t, J = 5 Hz, 4 H), 2.72 (t, J = 6 Hz, 2 H), 3.29 (t, J = 5 Hz, 4 H), 3.39 (m, 2 H), 5.88 (br s, exchangeable with D_2O, 1 H), 6.85 (s, 1 H), 7.01 (d, J = 8 Hz, 2 H), 7.38 (d, J = 8 Hz, 1 H), 7.61 (d, J = 8 Hz, 1 H), 7.79 (d, J = 8 Hz, 1 H), 7.93 (d, J = 8 Hz, 1 H), 8.06 (d, J = 8 Hz, 2 H); MS *m/z* (rel. int.) 58 (100), 389 (30, M^+). Anal. Calcd for $C_{24}H_{31}N_5$: C, 73.99; H, 8.02; N, 17.98. Found: C, 73.94; H, 8.03; N, 17.97.

N-[1-[2-(N-methylpiperazino)phenyl]ethylidene]-2-(trifluoromethyl)aniline (**23**). An oil; ^{1}H NMR δ 2.25 (s, 3 H), 2.41 (s, 3H), 2.65 (m, 4 H), 3.16 (m, 4 H), 6.75 (d, J = 8 Hz, 1 H), 7.13 (d, J = 8 Hz, 1 H), 7.14 (t, J = 8 Hz, 1 H), 7.18 (t, J = 8 Hz, 1 H), 7.39 (t, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 7.53 (t, J = 8 Hz, 1 H), 7.67 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 43 (100), 218 (20, M^+). Anal. Calcd for $C_{20}H_{22}F_3N_3$: C, 66.46; H, 6.13; N, 11.67. Found: C, 66.35; H, 6.18; N, 11.60.

4-(N-Methylpiperazino)-2-[2-(N-methylpiperazino)phenyl]quinoline (**24**). An oil; ^{1}H NMR (60 MHz) δ 2.25 (s, 3 H), 2.35 (m, 4 H), 2.46 (s, 3 H), 2.80 (m, 4 H), 2.95 (m, 4 H), 3.35 (m, 4 H), 7.05 - 8.35 (m and s at δ 7.70, 9 H); MS *m/z* (rel. int.) 331 (100), 401 (10, M^+). **24**•2HBr•H_2O: mp 338-339 °C. Anal. Calcd for $C_{25}H_{31}N_5$•3HBr•H_2O: C, 45.33; H, 5.47; N, 10.57. Found: C, 45.37; H, 5.48; N, 10.53.

6-Chloro-4-(N-methylpiperazino)-2-[2-(N-methylpiperazino)phenyl]quinoline (**26**). Mp 149-150 °C (from hexanes/95% EtOH); ^{1}H NMR (CD_2Cl_2) δ 2.36 (s, 3 H), 2.48 (br s, 4 H), 2.54 (s, 3 H), 2.86 (br s, 4 H), 3.04 (br s, 4 H), 3.43 (br s, 4 H), 7.27 (d, J = 8 Hz, 1 H), 7.28 (t, J = 8 Hz, 1 H), 7.53 (t, J = 8 Hz, 1 H), 7.73 (d, J = 8 Hz, 1 H), 7.78 (d, J = 8 Hz, 1 H), 7.85 (s, 1 H), 8.15 (d, J = 8 Hz, 1 H), 8.16 (s, 1 H); MS *m/z* (rel. int.) 365 (100), 435 (10, M^+). Anal. Calcd for $C_{25}H_{30}ClN_5$•0.5H_2O: C, 67.47; H, 7.02; N, 15.73. Found: C, 67.47; H, 7.00; N, 15.64.

2-(2-Chlorophenyl)-4-(N-methylpiperazino)quinoline (**28**). An oil; ^{1}H NMR δ 2.43 (s, 3 H), 2.74 (br s, 4 H), 3.33 (br s, 4 H), 7.19 (s, 1 H), 7.34 - 7.43 (m, 2 H), 7.48 - 7.54 (m, 2 H), 7.65 - 7.72 (m, 2 H), 8.06 (d, J = 8 Hz, 1 H), 8.12 (d, J = 8 Hz, 1 H); MS *m/z* (rel. int.) 70 (100), 337 (30, M^+), 339 (10, M^+). **28**•2HBr•H_2O: mp 275-277 °C. Anal. Calcd for $C_{20}H_{20}ClN_3$•2HBr•H_2O: C, 46.40; H, 4.67; N, 8.11. Found: C, 46.29; H, 4.73; N, 8.04.

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