Chemischen Industrie and I.C. the Swedish Natural Science Research Council (NFR) for financial support.

Registry No. 1·dioxane (1:1), 137092-83-2; 1·DMF (1:1), 137092-84-3; **2**, 137092-85-4; 2·DMF (3:1), 137092-86-5; 2-dioxane (4:1), 137092-87-6; **3**, 137092-88-7; 3·DMF (1:1), 137092-89-8; 3·diethylformamide (1:1), 137092-90-1; **4**, 137092-91-2; 4·MeOH (1:1), 137092-92-3; 4·EtOH (1:1), 137092-93-4; 4·DMF (1:1), 137092-94-5; 4·DMSO (1:2), 137092-95-6; 4·pyridine (1:1), 137092-96-7; **5**, 137092-97-8; 5·MeOH (1:1), 137092-98-9; 5·DMF (1:1), 137092-99-0; 5·diethylformamide (1:1), 137093-00-6; 5·DMSO (1:2), 137093-01-7; 5·pyridine (1:1), 137093-02-8; **6**, 137093-03-9; 6·acetone (4:1), 137093-04-0; 6·methylformamide (1:1), 137093-05-1; 6·DMF (1:1), 137093-06-2; 6·diethylformamide (1:1), 137093-07-3; 6·acetonitrile (2:1), 137093-08-4; 6·nitromethane (2:1), 137093-09-5; 6·THF (4:1), 137093-10-8; 6-dioxane (4:1), 137093-11-9; 6·pyridine (1:1), 137093-12-0; **7**, 137093-13-1; 7·MeOH (1:1), 137093-14-2; 7·EtOH (1:1), 137093-15-3; 7·acetic acid (1:1), 137093-16-4; 7·acetone (1:1), 137093-17-5; 7·DMF (1:1), 137093-18-6; 7·DMSO (1:1), 137093-19-7; **8**, 137093-20-0; 8·MeOH (1:1), 137093-21-1; 8·EtOH (3:1), 137093-22-2; 8·acetic acid (1:1), 137093-23-3; 8·DMF (1:1), 137093-24-4; 8·nitromethane (1:1), 137093-25-5; 8·THF (1:1), 137093-26-6; 8·dioxane (2:1), 137093-27-7; 8·pyridine (1:1), 137093-28-8; **9**, 137093-29-9; 9·DMF (1:1), 137093-30-2; 9·diethylformamide (1:1), 137093-31-3; 9·pyridine (1:1), 137143-55-6; **10**, 137093-32-4; 10·DMF (1:1), 137093-33-5; 10·diethylformamide (1:1), 137093-34-6; 10·dibutylformamide (1:1), 137093-35-7; 10·methylphenylformamide (1:1), 137093-36-8; 10·dimethylacetamide (1:1), 137093-37-9; 10·pyridine (1:1), 137093-38-0; **11**, 137093-39-1; 11·DMF (1:1), 137093-40-4; 11·DMF (1:2), 137093-41-5; 11·diethylformamide (1:1), 137093-42-6; 11·dimethylacetamide (1:1), 137093-43-7; 11·dioxane (1:1), 137093-44-8; 11·pyridine (1:1), 137093-45-9; **12**, 137093-46-0; **13**, 137093-47-1; 13·MeOH (1:1), 137093-48-2; **14**, 137122-26-0; 14·DMF (1:1), 137122-27-1; 14·THF (1:1), 137122-28-2; 14·dioxane (1:1), 137122-29-3; 14·pyridine (2:1), 137122-30-6; **15**, 137093-49-3; **16**, 137093-50-6; 16·dioxane (3:1), 137093-51-7; **17**, 137093-52-8; **18**, 137093-53-9; **19**, 137093-54-0; 19·acetonitrile (1:1), 137093-55-1; 19·nitromethane (1:1), 137093-56-2; **20**, 137093-57-3; **21**, 137093-58-4; 21·benzene (1:1), 137093-59-5; **22**, 137093-60-8; 22·DMF (1:1), 137093-61-9; 22·DMSO (1:1), 137093-62-0; 22·dioxane (2:1), 137093-63-1; 22·pyridine (1:1), 137093-64-2; **23**, 137093-65-3; 23·MeOH (1:1), 137093-66-4; 23·EtOH (1:1), 137093-67-5; 23·1-PrOH (2:1), 137093-68-6; 23·2-PrOH (2:1), 137093-69-7; 23·2-BuOH (3:1), 137093-70-0; 23·acetic acid (2:1), 137093-71-1; 23·propionic acid (2:1), 137093-72-2; 23·methylformamide (1:1), 137093-73-3; 23·DMF (1:1), 137093-74-4; 23·diethylformamide (1:1), 137093-75-5; 23·dimethylacetamide (1:1), 137093-76-6; 23·acetonitrile (1:1), 137122-31-7; 23·nitromethane (1:1), 137093-77-7; 23·nitroethane (1:1), 137093-78-8; 23·DMSO (1:1), 137093-79-9; 23·THF (1:1), 137093-80-2; 23·dioxane (2:1), 137093-81-3; 23·1,3-dioxolane (2:1), 137093-82-4; 23·tetrahydropyran (2:1), 137093-83-5; 23·pyridine (1:1), 137093-84-6; **24**, 137093-85-7; 24·MeOH (1:1), 137093-86-8; 24·EtOH (2:1), 137093-87-9; 24·2-PrOH (2:1), 137093-88-0; 24·methylformamide (1:1), 137093-89-1; 24·DMF (1:1), 137093-90-4; 24·dimethylacetamide (1:1), 137093-91-5; 24·nitromethane (1:1), 137093-92-6; 24·DMSO (2:1), 137093-93-7; 24·THF (1:1), 137093-94-8; 24·dioxane (2:1), 137093-95-9; 24·pyridine (2:1), 137093-96-0; **25**, 137093-97-1; 25·EtOH (1:1), 137093-98-2; 25·DMF (1:1), 137093-99-3; 25·dioxane (2:1), 137094-00-9; **26**, 137094-01-0; **27**, 137094-02-1; **28**, 137094-03-2; 28·THF (2:1), 137094-04-3; 28·DMF (1:1), 137094-05-4; **29**, 137094-06-5; **30**, 137094-07-6; 30·dioxane (2:1), 137094-08-7; **31**, 137122-32-8; **32**, 137094-09-8; **33**, 103515-22-6; aniline, 62-53-3; anthranilic acid, 118-92-3; 2-amino-5-methylbenzoic acid, 2941-78-8; 2-amino-5-chlorobenzoic acid, 635-21-2; 2-amino-4-chlorobenzoic acid, 89-77-0; 2-amino-3,5-dichlorobenzoic acid, 2789-92-6; 3-aminobenzoic acid, 99-05-8; 3-amino-4-methylbenzoic acid, 2458-12-0; 4-aminobenzoic acid, 150-13-0; 5-aminoisophthalic acid, 99-31-0; 4-hydroxyaniline, 123-30-8; 4-methoxyaniline, 104-94-9; 3-nitroaniline, 99-09-2; 4-nitroaniline, 100-01-6; 2-bromoaniline, 615-36-1; 4-bromoaniline, 106-40-1; 2-methylaniline, 95-53-4; 2,3-dimethylaniline, 87-59-2; 2,5-dimethylaniline, 95-78-3; 2,6-dimethylaniline, 87-62-7; glycine, 56-40-6; β-alanine, 107-95-9; 4-aminobutanoic acid, 56-12-2; 5-aminovalerianic acid, 660-88-8; 6-aminocaproic acid, 60-32-2; 4-aminophenylacetic acid, 1197-55-3; 4-(aminomethyl)benzoic acid, 56-91-7; aminoethanol, 141-43-5; diglycine, 556-50-3; 1,4-diaminobenzene, 106-50-3; benzidine, 92-87-5.

Supplementary Material Available: Spectroscopic (IR, ^{1}H NMR, MS) and elemental analytical data of the new compounds (Tables IV–VII), positional parameters of the non-hydrogen atoms (Table VIII), intramolecular bond lengths and bond angles involving non-hydrogen atoms (Table IX and X), positional parameters for the hydrogen atoms (Table XI), intramolecular bond lengths and bond angles involving hydrogen atoms (located from difference electron density maps; Table XII), and anisotropic temperature factors of the non-hydrogen atoms (Table XIII) (33 pages); tables of observed and calculated structure factors (44 pages). Ordering information is given on any current masthead page. A listing of observed and calculated structure factors is available directly from the authors.

Synthesis of Quinolines via Ortho-Lithiated *N*-Acylanilines. A Modified Friedländer Synthesis[1,2]

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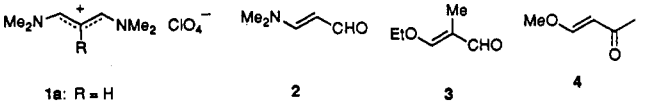
A new variation of the Friedländer quinoline synthesis was devised based on the sequential reaction of ortho-lithiated *N*-*t*-Boc-anilines or *N*-pivaloylanilines with masked malondialdehyde derivatives [e.g., vinamidinium salts **1a** and **1b**, 3-(dimethylamino)acrolein (**2**), and 3-ethoxymethacrolein (**3**)] and subsequent acid-induced cyclization.

The Friedländer quinoline synthesis involves the condensation of an aromatic *o*-amino aldehyde or *o*-amino ketone with an aldehyde or a ketone containing at least one methylene group α to the carbonyl moiety.[5-7] The

Scheme I



1a: R = H
1b: R = Ph

2 3 4

process is one of considerable breadth, but until recently (see below) a major limitation was that the *o*-amino car-

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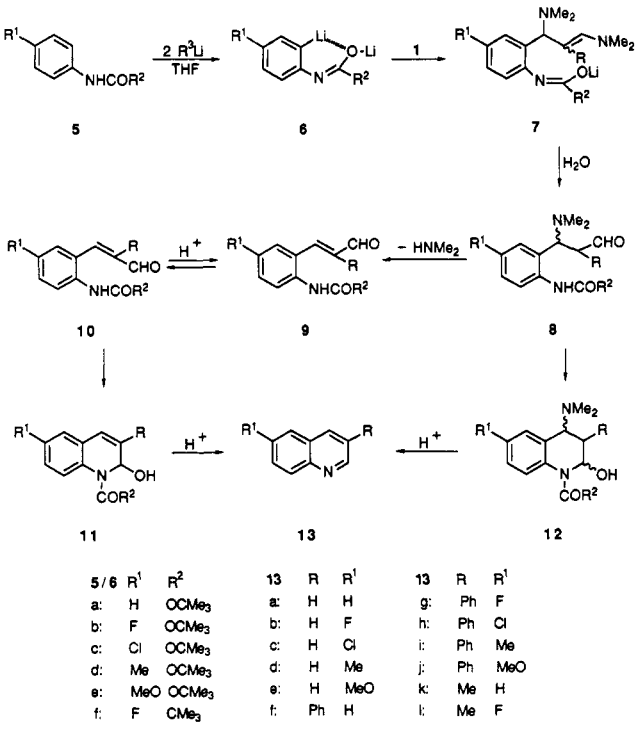
(2) Presented in part at the 74th Canadian Chemical Conference, Hamilton, Ont., Canada, June 2–6, 1991.
(3) Syntex Research Postdoctoral Fellow, 1989–1990.
(4) Syntex Research Postdoctoral Fellow, 1991–.
(5) Friedländer, P. *Ber.* **1882**, *15*, 2572.
(6) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.

0022-3263/91/1956-7288$02.50/0

Scheme II

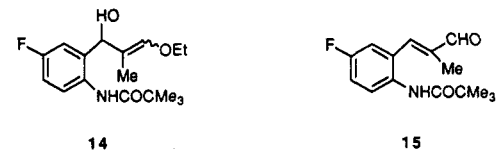


5/6	R^1	R^2	13	R	R^1	13	R	R^1
a:	H	$OCMe_3$	a:	H	H	g:	Ph	F
b:	F	$OCMe_3$	b:	H	F	h:	Ph	Cl
c:	Cl	$OCMe_3$	c:	H	Cl	i:	Ph	Me
d:	Me	$OCMe_3$	d:	H	Me	j:	Ph	MeO
e:	MeO	$OCMe_3$	e:	H	MeO	k:	Me	H
f:	F	CMe_3	f:	Ph	H	l:	Me	F

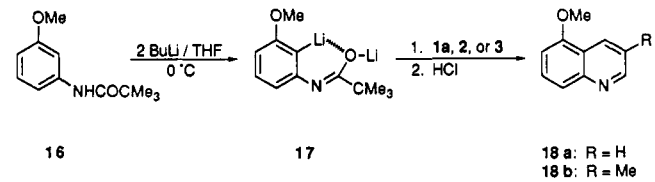
bonyl compounds were not readily accessible. This publication describes a new variation of the Friedländer quinoline synthesis which not only broadens its scope, but in addition, casts light on the mechanism of the acid-catalyzed modification of the reaction.

It occurred to us that a possible formal equivalent of the Friedländer synthesis might consist in the reaction of the dilithio species derived from an *N*-acylaniline with masked malondialdehyde derivatives such as **1–3** (Scheme I). The condensation of dilithiated *N*-(*tert*-butoxycarbonyl)anilines **6** (*N*-*t*-Boc-anilines)[8,9] with **1** (Scheme II) was elected for study first because of the ease of removal of the *t*-Boc group and the excellent electrophilicity of vinamidinium salts.[10] It was expected that aqueous hydrolysis of the primary adduct **7** would initially generate the aldehyde **8** which could either lose the elements of dimethylamine to generate the α,β-unsaturated *E*-aldehyde **9**, or cyclize to the hemiamidal **12**. The aromatization of **12** to the quinoline **13**, especially under acidic conditions, was expected to be facile,[11] and the ease of protonation of α,β-unsaturated aldehydes[12] boded well for the conversion of the *E*-aldehyde **9** to **13**, via the *Z*-aldehyde **10** and the hemiamidal **11**. In the event, addition of the solid vinamidinium perchlorate **1a**, at −20 °C, to a THF solution of the dilithio species derived from 4-chloro-*N*-*t*-Boc-aniline (**6c**) followed by quenching with aqueous sodium bicarbonate, gave a mixture which was shown by ^{1}H NMR spectroscopy to consist of the starting material **5c**, 6-chloroquinoline (**13c**), and the *E*-aldehyde **9** (R = H, R^1 = Cl, R^2 = $OCMe_3$). Column chromatographic separation

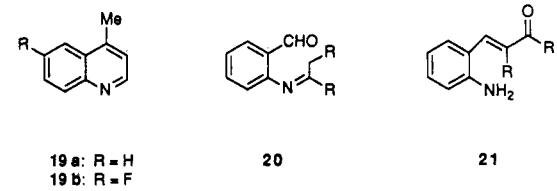
Scheme III



Scheme IV



Scheme V



of the mixture on silica gel provided the three compoents in 21, 37, and 43% yields, respectively. As predicted, the *E*-aldehyde underwent cyclization to 6-chloroquinoline, in ca. 80% yield, on treatment with acid under mild conditions (warming with dilute sulfuric acid in aqueous THF). For preparative purposes, the reaction mixture was quenched with excess trifluoroacetic acid and left at room temperature, to provide 6-chloroquinoline in over 60% yield (Table I). In a similar way, other 6-substitued quinolines and quinoline itself were prepared from the appropriate dilithiated *N*-*t*-Boc-anilines and **1a**. In addition, 3-phenylquinoline (**13f**)[13] and several 6-substitued 3-phenylquinolines (Table I) were synthesized in an entirely analogous manner from the phenyl-substituted vinamidinium salt **1b**.

The vinylogous formamide **2** also served as a malondialdehyde equivalent[14] in the above process, and quinoline (**13a**) and 6-fluoroquinoline (**13b**) were synthesized therefrom with acceptable efficiency (Table I). Here too the *E*-aldehyde **9** is involved as one of the intermediates, as demonstrated by ^{1}H NMR spectroscopy of the reaction mixture obtained on quenching with aqueous bicarbonate. In addition, utilization of the vinylogous ester **3**, a masked form of 2-methylmalondialdehyde,[14] in the above reaction sequence, readily gave 3-methylquinoline (**13k**) and the corresponding 6-fluoro compound **13l** (Table I).

Although *N*-pivaloylanilines (**5**, R^2 = CMe_3) are more easily ortho-lithiated than *N*-*t*-Boc-anilines,[15] the removal

(7) Jones, G. *The Chemistry of Heterocyclic Compounds. Quinoline. Part 1*; Jones, G., Ed.; John Wiley & Sons: London, 1977; pp 181–191.
(8) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
(9) Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725.
(10) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *J. Org. Chem.* **1990**, *55*, 4735 and references therein.
(11) Clark, R. D.; Muchowski, J. M.; Souchet, M.; Repke, D. B. *Synlett* **1990**, 207.
(12) Buchanan, J. G.; Hughes, N. A.; McQuillen, F. J.; Swan, G. A. *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier Publishing Co: Amsterdam, 1965; Vol. I. Aliphatic Compounds, Part C, pp 48–51.

(13) The composition (and probably the amount) of the solvent in which dilithio-*N*-*t*-Boc-aniline (**6a**) is generated has a pronounced effect on the quantity of quinoline or 3-phenylquinoline which is produced in these reactions. Thus, the original recipe[8] for the generation of this reagent, on a 10-mmol scale, used *tert*-butyllithium in pentane (12.0 mL of a 2 M solution) and THF (25 mL). These conditions correspond to those of method B (Experimental Section) and gave rise to quinoline and 3-phenylquinoline in 46 and 34% yields. If the amount of THF was increased to 270 mL (as in method A) the yield of these compounds dropped to less than 25%, presumably as a consequence of the destruction of the dilithio species in this solvent system. It is quite probable that had the lithiation of 4-methyl- (**5d**) and 4-methoxy-*N*-*t*-Boc-aniline (**5e**) been conducted under the conditions of method B, the corresponding quinolines would have been produced in yields considerably better than those given in Table I.
(14) These commercially available compounds are THF miscible and are thus more convenient to use than the rather insoluble vinamidinium salts.
(15) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.

Table I. Synthesis of Quinolines from *N*-(*tert*-Butoxycarbonyl)anilines or *N*-Pivaloylanilines and Masked Malondialdehyde Derivatives

N-acylaniline	masked malondialdehyde	lithiation conditions	product	% yield[a]	mp, °C observed	mp, °C reported
5a	**1a**	B[b]	**13a**	46	oil[c]	
5a	**2**	B	**13a**	43		
5b	**1a**	A	**13b**	90	oil	*d*
5b	**2**	B	**13b**	51		
5c	**1a**	A	**13c**	62	41–41.5	43[e]
5d	**1a**	A	**13d**	14	oil[c]	
5e	**1a**	A	**13e**	39	oil[c]	
5a	**1b**	B	**13f**	34	50.5–51.5	50–51[f]
5b	**1b**	A	**13g**	81	105–106	
5c	**1b**	A	**13h**	79	102.5–103.5	104.5[g]
5d	**1b**	A	**13i**	22	57–58	61[g]
5e	**1b**	A	**13j**	40	124–124.5	121–122[f]
5a	**3**	B	**13k**	56	oil[h]	
5b	**3**	B	**13l**	61	227–228[i]	
5f	**3**	C	**13l**	67		
16	**1a**	C	**18a**	58	oil	*j*
16	**2**	C	**18a**	45		
16	**3**	C	**18b**	87	238–240	
5a	**4**	B	**19a**	14	oil[c]	
5b	**4**	B	**19b**	17	oil	45[k]

[a] Yield of chromatographically homogeneous material. [b] See Experimental Section. [c] NMR spectrum identical to that of a commercial sample. [d] Reported[25] to have bp 116–118 °C (16 mm). [e] Reference 26. [f] Reference 27. [g] Reference 28. [h] NMR spectrum agrees with literature data.[29] [i] Mp of picrate. [j] Reported[30] to have bp 181–185 °C (14 mm). [k] Reference 31.

of the pivaloyl group can sometimes require quite vigorous conditions (e.g., 3 N HCl at reflux).[16] Nevertheless, if the *N*-pivaloyl- and *N*-*t*-Boc-anilines could be used interchangeably, the flexibility of this quinoline synthesis would be increased even further. Condensation of dilithio-*N*-pivaloyl-4-fluoroaniline (**6f**) with **3** and subsequent quenching of the reaction mixture with aqueous ammonium chloride gave a mixture of the *E*-aldehyde **15** and its precursor **14** (Scheme III). This aldehyde was not converted into 6-fluoroquinoline under the conditions used for the *t*-Boc analogues, but 1.5 N HCl in 50% aqueous dioxane at reflux temperature[16] did effect the transformation. Indeed, when the crude mixture of **14** and **15** was subjected to these conditions, **13l** was obtained in 67% yield.

5-Methoxyquinoline (**18a**, Scheme IV) can be prepared as a minor product from *m*-anisidine by a Skraup synthesis[17] or by other, less direct, several-step processes.[18,19] It is much more conveniently synthesized, however (Table I), using the methodology described herein, i.e., sequential reaction of dilithio-*N*-pivaloyl-3-methoxyaniline (**17**)[20] with **1a**[21] or **2** and cyclization with hot 1.5 N HCl. The corresponding 3-methyl compound **18b** can likewise be generated from **17** and **3** in 87% yield.

An attempt was made to utilize 4-methoxy-2-buten-1-one (**4**, Scheme I) as a source of 4-methylquinolines. The expected products **19a** and **19b** (Scheme V) were, in fact, obtained from the dilithiated *N*-*t*-Boc-anilines **6a** and **6b**, albeit in low yields (Table I). This result presumably stems from the acidity of the protons α to the carbonyl group in **4**. The condensation of the less basic dilithio-*N*-pivaloylanilines with **4** gave analogous results.

The Friedländer quinoline synthesis is generally accepted to occur by the initial formation of a Schiff base (e.g., **20**, Scheme V) followed by an internal aldol condensation.[7] An alternative mechanism involving initial generation of an aldol product (e.g., **21**) and subsequent cyclization is considered to be improbable, at least for the base-catalyzed version of the reaction, because *E* to *Z* isomerization of the unsaturated carbonyl system is unlikely under such conditions. The results described herein indicate, however, that *the latter mechanism cannot be discounted as a possibility for the acid-catalyzed Friedländer synthesis.*

In summary, a new version of the Friedländer quinoline synthesis, based on the condensation of ortho-lithiated *N*-acylanilines with masked malondialdehyde derivatives, was devised. The facility with which the unsaturated aldehydes **9** and **15** cyclize as well as the known ease of synthesis of *N*-acyl-*o*-aminoaryl aldehydes from ortho-lithiated *N*-acylarylamines[8,15,16] makes the Friedländer reaction even broader and one of the most versatile of all the quinoline syntheses.

Experimental Section

The physical constants of the compounds reported herein were obtained as described previously.[22]

The vinamidinium perchlorates **1a** and **1b** were prepared by the methods of Malhotra and Whiting[23] and Arnold,[24] respectively. Compounds **2**–**4** were commercial samples; the vinylogous amide **2** was distilled before use. The *N*-pivaloylanilines **5f** and **16** were synthesized as described by Fuhrer and Gschwend.[15]

All lithiation experiments were conducted under an atmosphere of dry nitrogen or argon.

Synthesis of the *N*-(*tert*-Butoxycarbonyl)anilines 5. Compounds **5b-e** were reported by Reed et al.[9] but no physical

(16) Turner, J. A. *J. Org. Chem.* **1990**, *55*, 4744.
(17) Peet, N. P.; Karrick, G. L.; Barbuch, R. J. *J. Heterocycl. Chem.* **1987**, *24*, 715.
(18) Fischer, O. *Ber.* **1882**, *15*, 1979.
(19) Tamura, Y.; Terashima, M.; Higuchi, Y.; Ozaki, K. *Chem. Ind. (London)* **1970**, 1435.
(20) *N*-*t*-Boc-3-methoxyaniline did not lithiate as cleanly or efficiently as the *N*-pivaloyl compound.
(21) 5-Methoxyquinoline was present in the crude reaction mixture even before HCl treatment.
(22) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
(23) Malhotra, S. S.; Whiting, M. C. *J. Chem. Soc.* **1960**, 3812.
(24) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
(25) Dockner, T.; Hagen, H.; Kohler, R-D.; Markert, J.; Ziegler, H. Ger. Offen DE 3326255, 1985; *Chem. Abstr.* **1986**, *104*, 19524m.
(26) von Braun, J.; Petzold, A.; Seeman, J. *Chem. Ber.* **1922**, *55*, 3779.
(27) Jutz, C.; Wagner, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 315.
(28) Todoriki, R.; Ono, M.; Tamura, S. *Heterocycles* **1986**, *24*, 755.
(29) McNab, H.; Murray, M. E.-A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 333.
(30) Tamura, Y.; Terashima, M.; Higuchi, Y.; Ozaki, K. *Chem. Ind. (London)* **1970**, 1435.
(31) Krainer, Z. Y.; Gudz, P. F.; Yagupolskii, L. M. *Chem. Heterocycl. Compd.* **1973**, 217.

constants thereof were given. They were prepared by the method[8] used to obtain **5a**, in 83–89% yields, and after crystallization from hexane had mps 135.5–136.5 °C, 125–127 °C, 94–95 °C, and 91.5–92.5 °C, respectively.

Lithiation of the *N*-Acylanilines 5 and 16. Method A. A solution of *tert*-butyllithium in pentane (7.1 mL of a 1.7 M solution; 12 mmol) was added to a stirred solution of the *N*-*t*-Boc-aniline (5 mmol) in anhydrous THF (130 mL) at −78 °C. The solution was then stirred for a further 1 h at −20 °C.

Method B. A solution of *tert*-butyllithium in pentane (7.1 mL of a 1.7 solution; 12 mmol) was added to a stirred solution of the *N*-*t*-Boc-aniline (5 mmol) in anhydrous THF (12.5 mL) at −78 °C. After 15 min at −78 °C, the solution was stirred at −20 °C for 2 h.

Method C. A solution of *n*-butyllithium in hexane (5.0 mL of a 2.5 M solution; 12.5 mmol) was added to a stirred solution of the *N*-pivaloylaniline (5 mL) in anhydrous THF (15 mL) at 0 °C. The solution was stirred for a further 2 h at 0 °C.

General Procedures for Synthesis of the Quinolines. A. From the *N*-(*tert*-Butoxycarbonyl)anilines. The masked malondialdehyde derivative (6 mmol) was added slowly, at −20 °C, to a stirred solution of the dilithio species (5 mmol) generated as described above. The solid vinamidinium salts **1a** and **1b** were added as such by means of a powder addition funnel. Compounds **2** and **3** were added as solutions in anhydrous THF (5 mL). The reaction mixture was then stirred at −20 °C for 2 h in the case of **1** and **3**. For reactions with the vinylogous amide **2**, the reaction mixture was stirred at −20 °C for 1 h and at room temperature overnight. The reaction mixture was quenched with excess trifluoroacetic acid (10 g, ca. 7 mL), and the solution was stirred at room temperature for 2 days. Excess dilute (5%) HCl was then added, and the acidic phase was separated and combined with an HCl extract of the organic phase. The aqueous acidic phase was made basic with saturated Na_2CO_3 solution, and the product was extracted into ether. The extract was dried over sodium sulfate and evaporated in vacuo. The residue was subjected to column chromatography on activity II neutral alumina using 5–10% ethyl acetate in hexane to elute the quinoline. Known quinolines were identified as indicated in Table I (see also below).

B. From the *N*-Pivaloylanilines. The masked malondialdehyde derivative **1a**, **2**, or **3** (6 mmol) was added, as described in A, to a stirred solution of the dilithio species **6f** or **17** (5 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 2 h, and then it was quenched by the addition of aqueous NH_4Cl. The products were extracted into ether, and the extract was washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was dissolved in a 1:1 mixture of dioxane (10 mL) and 3 N HCl (10 mL). This solution was heated at reflux temperature for 4 h, made basic with saturated sodium carbonate solution, and extracted with ether. The ether solution was extracted with 5% HCl, and the acid extract was made basic with Na_2CO_3 solution. The product was extracted into ether, and the extract was dried and evaporated in vacuo. The residue was subjected to column chromatographic resolution on Act II neutral alumina, the quinoline being eluted with ethyl acetate to hexane (1:9). Known quinolines were identified as indicated in Table I. In addition, the ^1H NMR spectral data of **13b**, **18a**, and **19b** are found in Table II (supplementary material).

C. Synthesis of the 4-Methylquinolines 19a and 19b. A solution of 4-methoxy-3-buten-2-one (6 mmol) in THF (5 mL) was added to a stirred solution of the dilithio species (**6a**, **6b**, or **6f**; 5 mmol) at −78 °C. The reaction mixture was then stirred at this temperature for 0.5 h and then, depending on whether an *N*-*t*-Boc-aniline or an *N*-pivaloylaniline had been used, the reaction mixture was processed as described in A or B above.

3-Phenyl-6-fluoroquinoline (13g). After crystallization from ether, it had mp 105–106 °C: NMR δ 7.43–7.56 (m, 5 H), 7.86–7.72 (m, 2 H, H-5,7), 8.13 (dd, 1 H, $J_{H,F}$ = 5.24 Hz, $J_{7,8}$ = 10.1 Hz, H-8), 8.24 (d, 1 H, $J_{2,4}$ = 2.24 Hz, H-4), 9.14 (d, 1 H, $J_{2,4}$ = 2.24 Hz, H-2). Anal. Calcd for $C_{15}H_{10}FN$: C, 80.70; H, 4.51; N, 6.27. Found: C, 80.59; H, 4.65; N, 6.14.

3-Methyl-6-fluoroquinoline (13l): oil; NMR δ 2.47 (d, 3 H, J = 1.11 Hz, Me), 7.28–7.41 (m, 2 H, H-5,7), 7.81 (bs, 1 H, H-4), 8.03 (dd, 1 H, $J_{H,F}$ = 5.37 Hz, $J_{7,8}$ = 9.1 Hz, H-8), 8.70 (bs, 1 H, H-2). The picrate was prepared in ethanol and on crystallization from acetone had mp 227–228 °C. Anal. Calcd for $C_{16}H_{11}FN_4O_7$: C, 49.23; H, 2.82; N, 14.36. Found: C, 49.57; H, 2.89; N, 14.28.

3-Methyl-5-methoxyquinoline (18b): oil; NMR δ 2.49 (s, 3 H, Me), 3.97 (s, 3 H, OMe), 6.80 (d, 1 H, $J_{6,7}$ = 7.62 Hz, H-6), 7.52 (t, 1 H, H-7), 7.64 (d, 1 H, $J_{7,8}$ = 8.79 Hz, H-8), 8.32 (bs, 1 H, H-4), 8.74 (d, 1 H, $J_{2,4}$ = 2.20 Hz, H-2). The picrate was prepared in ethanol and then crystallized from acetone, mp 238–240 °C. Anal. Calcd for $C_{17}H_{14}N_4O_8$: C, 50.75; H, 3.48; N, 13.93. Found: C, 50.38; H, 3.49; N, 13.96.

Generation of 2-((*tert*-Butoxycarbonyl)amino)-6-chlorocinnamaldehyde (9, R = H, R¹ = F, R² = OCMe₃). The dilithio species **6c** was generated, on a 5-mmol scale as described in method A above, and reacted with the vinamidinium salt **1a** (6 mmol) as indicated in general procedure A for the synthesis of quinolines. The reaction mixture was quenched with excess saturated $NaHCO_3$ and extracted with ether. The extract was dried over Na_2SO_4 and evaporated in vacuo, and the mixture thus obtained was separated by flash column chromatography on silica gel. Elution with ethyl acetate–hexane (15:85) gave the cinnamaldehyde (0.60 g, 43%) and starting material (0.24 g, 21%). Elution with ethyl acetate gave crude 6-chloroquinoline (0.30 g, 37%). Crystallization of the cinnamaldehyde from ethyl acetate–hexane gave pure material: mp 152–154 °C; NMR δ 1.52 (s, 9 H, $OCMe_3$), 6.44 (bs, 1 H, NH), 6.65 (dd, 1 H, J_{trans} = 15.88 Hz, $J_{H,CHO}$ = 7.56 Hz, C*H*CHO), 7.37 (dd, 1 H, J_o = 8.75 Hz, J_m = 2.40 Hz, H-4), 7.51 (d, 1 H, J_m = 2.40 Hz, H-6), 7.56 (d, 1 H, J_{trans} = 15.88 Hz, C*H*=CHCHO), 7.66 (bd, 1 H, J_o = 8.75 Hz, H-3), 9.74 (d, 1 H, $J_{H,CHO}$ = 7.56 Hz, CHO). Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.92; N, 4.97. Found: C, 59.78; H, 5.87; N, 4.67.

Generation of 1-[2-((*tert*-Butylcarbonyl)amino)-5-fluorophenyl]-2-methyl-3-ethoxy-2-propen-1-ol (14) and (*E*)-2-Methyl-3-[2-((*tert*-butylcarbonyl)amino)-5-fluorophenyl]-2-propenal (15). The dilithio species **6f** (5 mmol) was generated as described in method C and reacted with the methacrolein derivative **3** (6 mmol) as described in general procedure B. The reaction mixture was quenched with saturated $NaHCO_3$ (or NH_4Cl) and worked up as described in general procedure B. The crude product mixture was separated by flash column chromatography on silica gel, using ethyl acetate–hexane (1:3) as the eluant, to give the alcohol **14** (0.54 g, 35%) and the aldehyde **15** (0.18 g) contaminated with **14**. The enol ether **14** is converted into the aldehyde **15** on standing at room temperature. It had mp 79.5–81 °C: IR (CCl_4) 3624, 3406, 1680 cm^{-1}; NMR δ 1.20 (t, 3 H, J = 7.03 Hz, OCH_2Me), 1.22 (s, 9 H, CMe_3), 1.58 (bs, 1 H, C=CMe), 3.45 (bm, 1 H, OH), 3.73 (q, 2 H, J = 7.03 Hz, OCH_2Me), 5.08 (bs, 1 H, C*H*OH), 6.02 (m, 1 H, C=CH), 6.85 (dd, 1 H, $J_{H,F}$ = 9.3 Hz, J_m = 3.00 Hz, H-6), 6.92 (td, 1 H, H-4), 8.01 (dd, 1 H, J_o = 8.9 Hz, $J_{H,F}$ = 5.28 Hz, H-3), 9.02 (bs, 1 H, NH); high resolution MS calcd for $C_{17}H_{24}FNO_3$ 309.1740, found 309.1741.

The aldehyde **15**, after crystallization from ether–hexane had mp 111–112 °C: IR (KBr) 3440, 3387, 1673, 1629 cm^{-1}; NMR δ 1.31 (s, 9 H, CMe_3), 1.93 (d, 3 H, J = 1.3 Hz, C=CMe), 7.05 (dd, 1 H, J_{HF} = 9.0 Hz, J_m = 3.03 Hz, H-6), 7.11 (td, 1 H, H-4), 7.20 (bs, 1 H, NH), 7.26 (s, 1 H, C=CH), 7.82 (dd, 1 H, J_o = 8.88 Hz, $J_{H,F}$ = 5.26 Hz, H-3), 9.63 (s, 1 H, CHO). Anal. Calcd for $C_{15}H_{18}FNO_2$: C, 68.22; H, 6.84; N, 5.32. Found: C, 68.39; H, 7.01; N, 5.30.

Generation of 6-Chloroquinoline (13c) by Cyclization of Aldehyde 9 (R = H, R¹ = F, R² = OCMe₃). A solution of the aldehyde (0.600 g, 2 mmol) in THF (100 mL) and water (10 mL) containing concentrated sulfuric acid (5 drops) was heated at reflux temperature for 16 h. The reaction mixture was washed with 5% NaOH, dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (1:4) to elute 6-chloroquinoline (0.280 g, 78%), identical to the material obtained by the method described previously.

Supplementary Material Available: Table II containing spectral data of quinoline derivatives **13b**, **18a**, and **19b** (1 page). Ordering information is given on any current masthead page.