Versatile Synthesis of Dihydroquinolines and Quinoline Quinones Using Cyclobutenediones. Construction of the Pyridoacridine Ring System

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1-BOC-2-lithio-1,4-dihydropyridines were condensed with 3,4-disubstituted cyclobutenediones to produce 1,2-adducts. Neat thermolysis under oxygen-free conditions produced substituted 1,4-dihydroquinoline hydroquinones in which the *tert*-butoxy residue of the BOC group was displaced by a phenolic residue, generating an oxazolone ring that functioned to protect *both* rings of the dihydroquinoline hydroquinone from untimely oxidation. Oxidative aromatization with concomitant loss of the oxazolone ring was achieved using 2 equiv of *o*-chloranil in acetic acid and provided substituted quinoline quinones in good yields. By use of this strategy, a concise synthesis of the pyridoacridine ring system was achieved.

Introduction

Pyridoacridines are a family of marine alkaloids based on the 11*H*-pyrido[4,3,2-*mn*]acridine skeleton (**1**) (Figure 1),[2] many of which possess the "pyridoacridone" structure **2**. These compounds often exhibit an array of biological activities and a particular chemical behavior that have attracted the interest of many natural product chemists and biochemists. Since 1983, when the structure of amphimedine, the first of these marine alkaloids was reported,[3] many additional examples have been described, and a number of papers have appeared describing synthetic efforts toward and the total synthesis of pyridoacridine alkaloids.[4−14]

Building upon the well-established chemistry of cyclobutenediones **3**,[15−27] a direct synthetic entry to the biologically-active pyridoacridone ring system is depicted in eq 1. Addition of a suitably protected 4-(2-anilinyl)-2-lithiopyridine to a substituted cyclobutenedione would provide a 1,2-adduct that could be transformed into the pyridoacridone ring system **2** upon thermolysis, deprotection, and oxidation. However, a wide variety of 1,2-adducts derived from cyclobutenediones and 2-lithiated pyridines or other 2-lithiated azaaromatics produced ring-fused pyridones, exclusively (eq 2), by attack of the

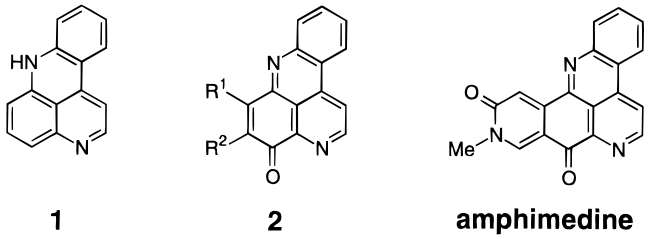

Figure 1.

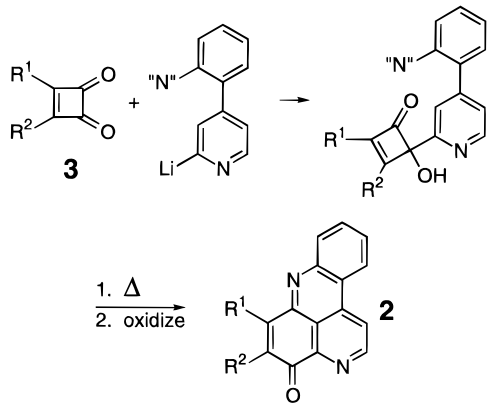

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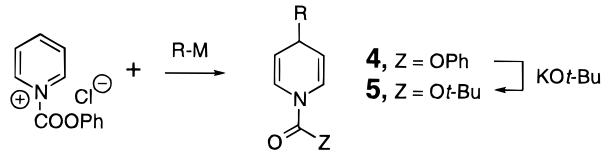
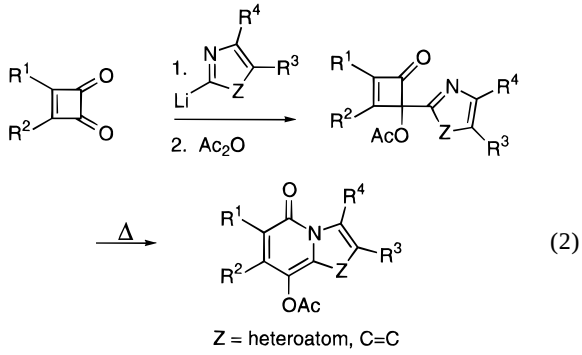
Table 1. Synthesis of 1,4-Disubstituted 1,4-Dihydropyridines



entry	RM	R	compd	condns[b] **4** → **5**	compd	yield (%)
1	$NaBH_4$	H	**4a**	A	**5a**[40]	41
2	MeMgCl[a]	Me	**4b**	B	**5b**[28]	87
3	nBuMgCl[a]	nBu	**4c**	B	**5c**[28]	81
4	PhMgCl[a]	Ph	**4d**	C	**5d**	85
5	2-$MeOC_6H_4MgCl$[a]	2-$MeOC_6H_4$	**4e**	C	**5e**	85
6	$(2\text{-}FC_6H_4)_2CuLi$	2-FC_6H_4	**4f**	C	**5f**	86
7	$[4\text{-}(allyl)_2NC_6H_4]_2CuLi$	4-$(allyl)_2NC_6H_4$	**4g**	C	**5g**	78

[a] 5 mol % CuI. [b] A: THF, rt. B: THF, −20 °C. C: toluene, −78 °C.

electron-rich nitrogen atom upon the ketene intermediate that is formed during thermolysis.[19,23]



(2)

In order to circumvent the undesired interaction between the nucleophilic nitrogen atom and the electrophilic central carbon atom of the ketene, a cyclobutenedione-based route to quinoline quinones demands the use of a 2-lithiopyridine equivalent that lacks a nucleophilic nitrogen atom. *N*-BOC-protected 1,4-dihydropyridines are easily prepared and are readily lithiated at the 2-position and then functionalized with electrophiles.[28,29] These represent appropriate synthetic equivalents of pyridines for the projected quinoline quinone synthesis. The BOC protecting group provides activation for the metalation step and attenuates the nucleophilicity of the nitrogen atom, thus preventing undesired attack on the ketene intermediate that is generated during the thermal ring opening of the cyclobutenone. N-Deprotection is easily effected, thereby allowing facile aromatization. Reported herein is an efficient strategy for the preparation of substituted dihydroquinolines and the medicinally important quinoline quinone ring system[30−32] *via* the regioselective addition of 1-BOC-2-lithio-1,4-dihydropyridines to 3,4-disubstituted cyclobutenediones. An application of this methodology to the synthesis of the pyridoacridine ring system is described.

Results and Discussion

The chemistry of dihydropyridines has been extensively studied.[33,34] Among the various methods known for their preparation, the nucleophilic addition of organometallic reagents to pyridinium salts provides good yields and in some cases occurs with high regioselectivity. Therefore, the direct addition of organometallic reagents (Mg, Li, Sn) to 1-acylpyridinium salts usually produces 1,2-dihydropyridines.[35−37] However, reaction of 1-acylpyridinium salts with lithium dialkyl- or diarylcuprates provides the isomeric 4-alkyl(aryl)-1,4-dihydropyridines.[38] Comins reported an improved method for the preparation of 4-substituted 1-acyl-1,4-dihydropyridines via the regioselective addition of Grignard reagents to 1-acylpyridinium salts in the presence of catalytic amounts of CuI.[39]

A number of 4-substituted 1,4-dihydropyridines were prepared using both the addition of lithium diarylcuprates to 1-(phenoxycarbonyl)pyridinium chloride and the Comins[28] procedure (Table 1). The resulting crude 1-(phenoxycarbonyl)-1,4-dihydropyridines were treated with potassium *tert*-butoxide and converted into the more robust *N*-BOC derivatives prior to α-metalation with alkyllithium bases. Using this protocol, the 4-*alkyl*-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines were prepared in very good yields as the only isolated regioisomers. Unexpectedly, however, when 1-(phenoxycarbonyl)-4-*phenyl*-1,4-dihydropyridine was treated with potassium *tert*-butoxide in THF at various temperatures, a mixture of the 1,2- and 1,4-regioisomers was obtained in which the 1,2-dihydropyridine predominated. Since 1,4-dihydropyridines are reported to be more stable than their 1,2-regioisomers (the latter isomerize to the former under basic conditions),[40,41] it is presumed that π-electron delocalization with the 4-phenyl substituent increases the thermodynamic stability of the 1,2-isomer relative to the 1,4-isomer. This problem was solved by conducting the PhOCO to *t*-BuOCO exchange reaction in toluene at −78 °C. Under these conditions, urethane exchange occurred to the exclusion of base-catalyzed double-bond isomerization, and the desired 4-aryl-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines were produced in good yields (Table

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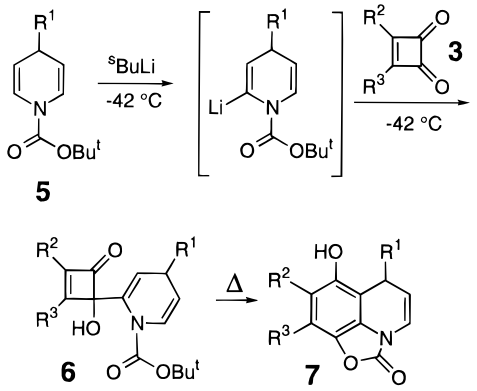
Table 2. Synthesis of 1,4-Dihydroquinoline Hydroquinones



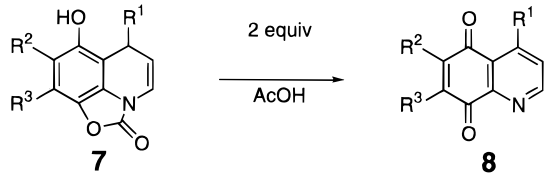
entry	5	R^1	3	R^2	R^3	compd	yield (%)
1	**5a**	H	**3a**	^{i}PrO	^{i}PrO	**7a**	53
2	**5a**	H	**3d**	4-FC_6H_4	^{i}PrO	**7b**	44
3	**5b**	Me	**3a**	^{i}PrO	^{i}PrO	**7c**	55
4	**5b**	Me	**3b**	Et	Et	**7d**	65
5	**5b**	Me	**3c**	Me	^{i}PrO	**7e**	42
6	**5b**	Me	**3d**	4-FC_6H_4	^{i}PrO	**7f**	74
7	**5c**	^{n}Bu	**3a**	^{i}PrO	^{i}PrO	**7g**	65
8	**5c**	^{n}Bu	**3c**	Me	^{i}PrO	**7h**	55
9	**5d**	Ph	**3a**	^{i}PrO	^{i}PrO	**7i**	60
10	**5d**	Ph	**3c**	Me	^{i}PrO	**7j**	41
11	**5e**	2-$MeOC_6H_4$	**3a**	^{i}PrO	^{i}PrO	**7k**	57
12	**5f**	2-FC_6H_4	**3a**	^{i}PrO	^{i}PrO	**7l**	53
13	**5g**	4-$(allyl)_2NC_6H_4$	**3b**	Et	Et	**7m**	62

1, entries 4−7). In the preparation of 4-*unsubstituted* 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine, the base-catalyzed equilibration between the 1,2- and 1,4-regioisomers was employed to advantage. The mixture of 1,4- and 1,2-dihydropyridines that is formed on reduction of 1-(phenoxycarbonyl)pyridinium chloride with sodium borohydride was equilibrated in the presence of potassium *tert*-butoxide in THF at room temperature and produced compound **5a** in 41% yield (Table 1, entry 1).[40,42]

Because most of the dihydropyridines investigated in this study were not stable upon standing, **5a**−**g** were prepared immediately prior to use. Treatment of 4-substituted 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines **5** with *sec*-butyllithium in THF at −42 °C generated the 2-lithio derivatives, which reacted with a variety of 3,4-disubstituted 3-cyclobutenediones **3** at the most electrophilic carbonyl group to produce the 1,2-adducts, **6**. The crude adducts **6** were degassed under vacuum and then heated neat at 160−165 °C for up to 60 min under an oxygen-free atmosphere to produce the highly-substituted 1,4-dihydroquinoline hydroquinones **7** in moderate to good yields (Table 2). Rigorous maintenance of oxygen-free conditions was essential during the thermolysis in order to prevent the formation of complex reaction mixtures. During this process the 4-hydroxyl substituent on the cyclobutenone ring displaced the *tert*-butoxy residue of the BOC group generating an oxazolone ring, which functioned to protect *both* rings of the dihydroquinoline hydroquinone from untimely oxidation. Results are summarized in Table 2.

Oxidative aromatization of the N-substituted 1,4-dihydroquinoline hydroquinones **7** using 2 equiv of *o*-chloranil in acetic acid[28] proceeded efficiently with concomitant loss of the oxazolone ring and provided the substituted quinoline quinones **8** in good yields (Table 3).

Table 3. Oxidation of 1,4-Dihydroquinoline Hydroquinones to Quinoline Quinones



entry	7	R^1	R^2	R^3	compd	yield (%)
1	**7c**	Me	^{i}PrO	^{i}PrO	**8c**	55
2	**7e**	Me	Me	^{i}PrO	**8e**	47
3	**7g**	^{n}Bu	^{i}PrO	^{i}PrO	**8g**	93
4	**7h**	^{n}Bu	Me	^{i}PrO	**8h**	73
5	**7i**	Ph	^{i}PrO	^{i}PrO	**8i**	62
6	**7j**	Ph	Me	^{i}PrO	**8j**	82
7	**7k**	2-$MeOC_6H_4$	^{i}PrO	^{i}PrO	**8k**	77
8	**7l**	2-FC_6H_4	^{i}PrO	^{i}PrO	**8l**	82

Construction of the Pyridoacridine Ring. Almost all the members of pyridoacridine family of marine alkaloids are cytotoxic, and some exhibit specific properties such as inhibition of topoisomerase II,[43] anti-HIV activity,[44] Ca^{2+} release activity,[45] metal-chelating properties,[46] or intercalation into DNA.[46] Different approaches to the synthesis of these polycyclic alkaloids have been reported in the last few years,[4−8] and the efforts toward the synthesis of their polycyclic skeletons and related pyridoacridines are considerable.[9−14] Because of the importance that pyridoacridines have acquired since their discovery, a general synthetic route to pyridoacridines would be of great interest and potential utility in medicinal chemistry.

A concise synthesis of the pyridoacridine ring system that is based on the quinoline quinone synthesis described above is depicted in Scheme 1. The key tactical issue was selection of an appropriate aniline nitrogen-protecting group that would survive exposure to the strong nucleophiles and bases (RMgX, RLi) required for formation of the 4-substituted 1,4-dihydropyridine and its subsequent metalation. The 2,5-dimethylpyrrole group fulfilled this role.[47]

Condensation of 2-bromoaniline with 2,5-hexanedione in the presence of a catalytic amount of acetic acid produced *N*-(2-bromophenyl)-2,5-dimethylpyrrole (**9**) in quantitative yield. Copper-mediated addition of the Grignard reagent derived from **9** to $C_5H_5NCO_2Ph^+Cl^-$ provided the protected 4-(2-anilinyl)-1,4-dihydropyridine **10**, which was treated with 2 equiv of potassium *tert*-butoxide in toluene at −78 °C to produce the protected 4-(2-anilinyl)-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine **11** as the only regioisomer in 86% overall yield. Lithiation of dihydropyridine **11** in the presence of 2 equiv of *sec*-butyllithium at −78 °C over 5 h followed by condensation with 3,4-diisopropoxy-3-cyclobutenedione (**3a**) at −78 °C directly afforded the 1,2-adduct as the

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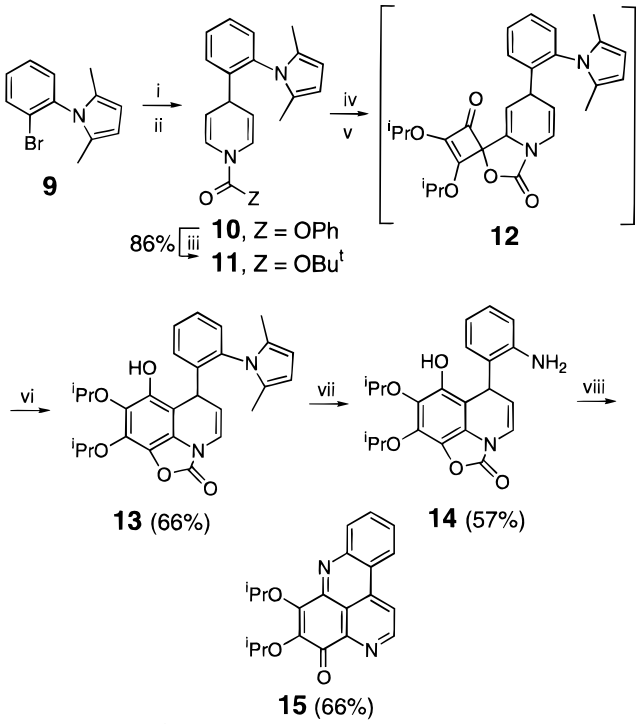
Scheme 1[a]



[a] Key: (i) Mg, THF, reflux; (ii) $C_5H_5NCO_2Ph^+Cl^-$, 5% CuI, −23 °C; (iii) KO^{t}Bu, toluene, −78 °C; (iv) ^{s}BuLi, THF, −78 °C; (v) **3a**, −78 °C; (vi) heat; (vii) $NH_2OH{\cdot}HCl$, Et_3N, NBS, EtOH:H_2O; (viii) ^{t}BuOOH, KOH, EtOH.

oxazolone **12**. The crude reaction product was degassed under vacuum and heated neat at 160−165 °C for 45 min under oxygen-free conditions to produce dihydroquinoline hydroquinone **13** in good yield (66% overall from **11**).

Primary amines have been generated from N-substituted 2,5-dimethylpyrroles by treatment with hydroxylamine hydrochloride under pH-dependent conditions (Et_3N, *i*-PrOH/water).[48] However, attempts to deprotect the anilino nitrogen of **13** under these and related conditions resulted in recovery of unreacted pyrrole or complex reaction mixtures. On the basis of the assumption that hydrolysis of the 2,5-dimethylpyrrole ring hydrolysis might be facilitated through bromonium ion formation, the hydroxylamine hydrochloride deprotection procedure was attempted in the presence of *N*-bromosuccinimide as a co-reagent. Using this protocol (20 equiv of $NH_2OH{\cdot}HCl$, 10 equiv of Et_3N, 2 equiv of NBS, EtOH/water), removal of the 2,5-dimethylpyrrole ring of **13** could be achieved in 57% yield. Starting material (30%) was recovered, but the yield of the desired product, **14**, could not be increased through the use of larger amounts of NBS and/or longer reaction times.

Oxidation of the dihydroquinoline hydroquinone **14** and condensation to the pyridoacridone did not take place using *o*-chloranil in acetic acid or other solvents. However, on treatment of **14** with excess *tert*-butyl hydroperoxide in ethanol/KOH, oxidation and spontaneous condensation took place, giving the pyridoacridone **15** in 66% yield or 21% overall yield from 2-bromoaniline. A variety of substituted pyridoacridines should be accessible either by varying the cyclobutenedione or by direct functionalization of **15**.

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Conclusions

A general synthesis of 4,6,7-substituted quinoline-5,8-quinones was developed beginning with the condensation of 2-lithio-*N*-BOC-1,4-dihydropyridines with cyclobutenediones. The synthesis is completed by thermolysis of the 1,2-adduct followed by oxidation of the resulting dihydroquinoline hydroquinone with chloranil in acetic acid. By use of this strategy, a concise synthesis of the pyridoacridine ring system was achieved.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in deuteriochloroform ($CDCl_3$) using chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) as the internal reference, unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished by one or more of the following methods: UV light, phosphomolybdic acid stain, vanillin stain, and anisaldehyde stain. Solvents for extraction and chromatography were reagent grade and used as received. Chromatographic purification was conducted by flash column chromatography and Baeckström column chromatography[49] using 32−63 μm flash silica gel obtained from EM. Solvents (THF, toluene) were dried over 4 Å molecular sieves before use and had no more than 50 ppm of H_2O as measured by Karl Fischer titration. Reagents purchased from commercial sources were used directly without further purification. All reactions were performed under a dry argon or nitrogen atmosphere in base-washed, flame-dried glassware. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl and $NaHCO_3$ refer to saturated aqueous solutions.

Starting Materials. The following starting materials were prepared according to literature procedures: 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine,[40] 1-(*tert*-butoxycarbonyl)-4-methyl-1,4-dihydropyridine,[28] 1-(*tert*-butoxycarbonyl)-4-*n*-butyl-1,4-dihydropyridine,[28] 3,4-diisopropoxy-3-cyclobutene-1,2-dione,[50] 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione,[50] 3,4-diethyl-3-cyclobutene-1,2-dione,[50] 4-(4-fluorophenyl)-3-isopropoxy-3-cyclobutene-1,2-dione.[50]

Dihydropyridine Synthesis. Because most of the dihydropyridines investigated in this study were not stable upon standing, **5a**−**g** were prepared immediately prior to use.

1-(*tert*-Butoxycarbonyl)-4-phenyl-1,4-dihydropyridine (5d). Pyridine (3.00 mL, 37.09 mmol, 1.50 equiv) and CuI (235 mg, 1.23 mmol, 0.05 equiv) were dissolved in THF (50 mL) at −23 °C in a 250 mL round-bottomed flask. Phenyl chloroformate (3.87 g, 24.72 mmol, 1.00 equiv) was added dropwise with stirring. After 5 min, phenylmagnesium chloride (12.36 mL, 2.0 M in THF, 24.73 mmol, 1.00 equiv) was added via syringe pump over 40 min, and the resulting solution was stirred at −23 °C for 30 min. After being warmed to room temperature and stirred at that temperature for another 20 min, the reaction mixture was partitioned between aqueous NH_4Cl (20%, 35 mL) and Et_2O (250 mL). The organic layer was washed with NH_4Cl (25 mL), water (25 mL), 10% HCl (2 × 25 mL), and water (3 × 25 mL) and then dried ($MgSO_4$), filtered, and evaporated, leaving 6.76 g of a yellow solid. A portion of the crude solid (1.84 g) was dissolved in toluene (45 mL) and cooled to −78 °C in a 100 mL round-bottomed flask. Potassium *tert*-butoxide in THF (19.90 mL, 1.00 M, 19.90 mmol, 3.00 equiv) was added dropwise, and the reaction mixture was stirred at −78 °C for 1.5 h. The reaction mixture was quenched with water and then partitioned between water (25 mL) and Et_2O (50 mL). The layers were separated, and the organic layer was washed with 5% NaOH (2 × 25 mL) and water (3 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated to a clear yellow oil. Chromatographic purifica

(49) Purchased from Baeckström SEPARO AB, Larsbergsvägen 24, S-181 39 Lindingö, Sweden.

(50) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.

tion (Flash column, silica gel, 2.5 cm × 10 cm, 10% EtOAc/hexanes) gave 1-(*tert*-butoxycarbonyl)-4-phenyl-1,4-dihydropyridine as a colorless oil (2.55 g, 8.87 mmol, 85%): TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.72$); IR (neat, KBr pellet, cm^{-1}) 3060 (w), 3028 (w), 2978 (s), 1718 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.20 (m, 5 H), 6.96 (d, $J = 7.2$ Hz, 1 H), 6.80 (d, $J = 6.6$ Hz, 1 H), 4.96 (br s, 1 H), 4.88 (br s, 1 H), 4.20−4.19 (m, 1 H), 1.55 (s, 9 H).

1-(*tert*-Butoxycarbonyl)-4-(2-methoxyphenyl)-1,4-dihydropyridine (5e). Magnesium turnings (0.30 g, 12.51 mmol, 1.20 equiv) and I_2 (5 mg) were mixed together and flamed under vacuum for 5−10 s in a 250 mL three-necked, round-bottomed flask equipped with an addition funnel and condenser. 2-Bromoanisole (1.86 mL, 10.46 mmol, 1.00 equiv) was added dropwise, initially just a few drops neat, and then the remainder diluted in THF (10 mL). After 5 h, the resulting black solution was cannulated into a freshly prepared mixture of pyridine (1.26 mL, 15.58 mmol, 1.49 equiv), copper(I) iodide (99 mg, 10.44 mmol, 0.05 equiv), and phenyl chloroformate (1.31 mL, 10.440 mmol, 1.00 equiv) in THF (10 mL) cooled to −23 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was partitioned between saturated NH_4Cl (20 mL) and Et_2O (50 mL) and the layers were separated. The organic layer was washed with 1:1 NH_4Cl/NH_4OH (40 mL), water (20 mL), 10% HCl (20 mL), and water (2 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated to a yellow oil (3.20 g). Potassium *tert*-butoxide in THF (20.89 mL, 1.00 M, 20.89 mmol, 2.00 equiv) was added dropwise to a solution of the crude product in toluene (100 mL) at −78 °C. After being stirred at −78 °C for 1.5 h, the reaction mixture was quenched with water and then partitioned between water (35 mL) and ether (100 mL). The layers were separated, and the organic layer was washed with 5% NaOH (2 × 35 mL) and water (2 × 25 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil that was purified by chromatography (flash column, silica gel, 2.5 cm × 10 cm, 10% EtOAc/hexanes) to give 1-(*tert*-butoxycarbonyl)-4-(2-methoxyphenyl)-1,4-dihydropyridine as a colorless oil (2.55 g, 8.87 mmol, 85%): TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.49$); IR ($CDCl_3$, KCl, cm^{-1}) 2983 (s), 2939 (s), 2250 (m), 1704 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (dd, $J = 7.5$, 1.5 Hz, 1 H), 7.20 (dt, $J = 7.8$, 1.5 Hz, 1 H), 6.98 (app t, $J = 7.5$ Hz, 1 H), 6.87−6.78 (m, 3 H), 4.98−4.90 (m, 2 H), 4.62−4.60 (m, 1 H), 3.83 (s, 3 H), 1.52 (s, 9 H).

1-(*tert*-Butoxycarbonyl)-4-(2-fluorophenyl)-1,4-dihydropyridine (5f). *n*-Butyllithium (14.77 mL, 1.60 M in hexane, 23.63 mmol, 2.20 equiv) was added dropwise to a solution of 2-fluorobromobenzene (3.76 g, 21.48 mmol, 2.00 equiv) dissolved in THF (50 mL) at −78 °C. After 40 min, copper (I) iodide (2.05 g, 10.76 mmol, 1.00 equiv) was added in one portion. The reaction mixture was stirred at −78 °C for 10 min and then warmed to 0 °C. After 1 h, the green solution was cannulated into a freshly prepared solution of pyridine (1.30 mL, 16.07 mmol, 1.50 equiv) and phenyl chloroformate (1.35 mL, 10.76 mmol, 1.00 equiv) in THF (50 mL) cooled to −23 °C. After 30 min, the reaction mixture was allowed to warm to room temperature and then quenched with NH_4Cl (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with 1:1 NH_4Cl/NH_4OH (100 mL), water (50 mL), 10% HCl (50 mL), and water (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated to a yellow oil (3.40 g). The crude product was dissolved in 100 mL of toluene, cooled to −78 °C, and treated dropwise with a solution of potassium *tert*-butoxide in THF (19.33 mL, 1.00 M, 19.33 mmol, 1.80 equiv). After 1.5 h, the reaction mixture was quenched with water and then partitioned between water (35 mL) and Et_2O (200 mL). The layers were separated, and the organic layer was washed with 5% NaOH (2 × 50 mL) and water (3 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Chromatographic purification (flash column, silica gel, 2.5 cm × 10 cm, 10% EtOAc/hexanes) gave 1-(*tert*-butoxycarbonyl)-4-(2-fluorophenyl)-1,4-dihydropyridine as a colorless oil (2.54 g, 9.23 mmol, 86%): TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.62$); IR (neat, KCl, cm^{-1}) 2978 (s), 2932 (m), 1723 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51−6.96 (m, 5 H), 6.81 (br s, 1 H), 4.91 (br s, 1 H), 4.85 (br s, 1 H), 4.55 (m, 1 H), 1.51 (s, 9 H).

1-(*tert*-Butoxycarbonyl)-4-[4-(*N*,*N*-diallylamino)phenyl]-1,4-dihydropyridine (5g). *n*-Butyllithium (1.87 mL, 2.20 M in hexane, 4.11 mmol, 2.00 equiv) was added dropwise to a −78 °C solution of 4-bromo-*N*,*N*-diallylaniline[51] (1.04 g, 4.12 mmol, 2.00 equiv) dissolved in THF (20 mL) in a 50 mL round-bottomed flask. After 30 min, copper(I) iodide (0.39 g, 2.05 mmol, 1.00 equiv) was added in one portion. The reaction mixture was allowed to warm to room temperature and then cannulated into a freshly prepared solution of pyridine (0.25 mL, 3.09 mmol, 1.50 equiv) and phenyl chloroformate (0.26 mL, 2.06 mmol, 1.00 equiv) in THF cooled to −23 °C. After 1 h, the reaction was quenched with NH_4Cl (20 mL), and the organic layer was washed with 1:1 NH_4Cl/NH_4OH (40 mL), water (20 mL), 10% HCl (20 mL), and water (2 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated to a yellow oil (0.70 g). The crude product was dissolved in 50 mL of toluene, cooled to −78 °C, and treated dropwise with a solution of potassium *tert*-butoxide in THF (5.60 mL, 1.00 M, 5.60 mmol, 2.72 equiv). After 1.5 h, the reaction mixture was partitioned between water (35 mL) and Et_2O (200 mL). The organic layer was washed with 5% NaOH (2 × 50 mL) and water (3 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Chromatographic purification (flash column, silica gel, 1.5 cm × 10 cm, 5% EtOAc/hexanes) gave 1-(*tert*-butoxycarbonyl)-4-[4-(*N*,*N*-diallylamino)phenyl]-1,4-dihydropyridine as a colorless oil (0.56 g, 1.59 mmol, 78%): TLC (silica gel, 15% EtOAc/hexanes, $R_f = 0.50$); IR (neat, KCl, cm^{-1}) 2967 (m), 2930 (m), 1727 (w), 1603 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, $J = 8.4$ Hz, 2 H), 6.90−6.76 (m, 2 H), 6.67 (d, $J = 8.4$ Hz, 2 H), 5.90−5.79 (m, 2 H), 5.21−5.14 (m, 4 H), 4.95−4.84 (m, 2 H), 4.05−4.04 (m, 1 H), 3.91−3.89 (m, 4 H), 1.53 (s, 9 H).

1,4-Dihydroquinolines by Condensation of 2-Lithiodihydropyridines and Cyclobutenediones. 1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-1,4-dihydroquinoline (7a). *sec*-Butyllithium (2.29 mL, 1.30 M in cyclohexane, 2.98 mmol, 1.10 equiv) was added dropwise to a −78 °C solution of 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine (**5a**) (0.49 g, 2.70 mmol, 1.00 equiv) in THF (15 mL). The reaction mixture was warmed to −42 °C, held at that temperature for 3 h, and then cannulated into a −78 °C solution of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**3a**) (0.54 g, 2.72 mmol, 1.01 equiv) in THF (10 mL). After 2 h, the reaction mixture was quenched with NH_4Cl (35 mL), allowed to warm to room temperature, and extracted with ether (3 × 25 mL). The combined organic layers were washed with water (3 × 25 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil. The crude product was degassed (six cycles, nitrogen−vacuum−nitrogen) and placed into a hot oil bath (160−165 °C) for 1 h. Chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-1,4-dihydroquinoline as a white solid (0.44 g, 1.44 mmol, 53%): mp 79−80 °C (EtOAc/hexane); TLC (silica gel, 10% EtOAc/hexanes, $R_f = 0.63$); IR (CH_2Cl_2, KCl, cm^{-1}) 3512 (m), 3056 (s), 2989 (s), 1779 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66−6.32 (m, 1 H), 5.81 (s, 1 H), 5.25−5.22 (m, 1 H), 4.83 (sept, $J = 6.0$ Hz, 1 H), 4.46 (sept, $J = 6.0$ Hz, 1 H), 3.45 (dd, $J = 3.3$, 2.4 Hz, 1 H), 1.31 (d, $J = 6.0$ Hz, 6 H), 1.25 (d, $J = 6.0$ Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.7, 144.7, 134.3, 132.8, 124.1, 123.0, 118.2, 110.0, 96.7, 76.2, 74.5, 22.6, 22.4, 21.1. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.81; H, 6.29; N, 4.57.

1,8-(Carbonyloxy)-6-(4-fluorophenyl)-5-hydroxy-7-isopropoxy-1,4-dihydroquinoline (7b). Following the procedure for **7a**, above, 1-(*tert*-butoxycarbonyl)-1,4-dihydopyridine (**5a**) (0.34 g, 1.88 mmol, 1.00 equiv) in THF (15 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (1.59 mL, 1.30 M in cyclohexane, 2.07 mmol, 1.10 equiv) and condensed with 4-(4-fluorophenyl)-3-isopropoxy-3-cyclobutene-1,2-dione (**3d**) (0.44 g, 1.88 mmol, 1.00 equiv) in THF (20 mL) at −78

(51) Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685.

°C. Workup, thermolysis neat (160−165 °C, 1 h), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6-(4-fluorophenyl)-5-hydroxy-7-isopropoxy-1,4-dihydroquinoline as a white solid (0.28 g, 0.82 mmol, 44%): mp 186−187 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.19$); IR (CH_2Cl_2, KCl, cm^{-1}) 3541 (m), 2983 (m), 1781 (s), 1388 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.25 (m, 2 H), 7.18 (t, J = 8.1 Hz, 2 H), 6.73 (dt, J = 8.1, 2.1 Hz, 1 H), 5.37−5.32 (m, J = Hz, 1 H), 4.85 (s, 1 H), 4.75 (sept, J = 6.0 Hz, 1 H), 3.52 (m, 2 H), 1.15 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.9, 150.7, 147.5, 138.0, 133.0, 132.9, 128.1, 127.9, 124.4, 118.2, 116.3, 116.0, 115.1, 110.6, 97.7, 74.4, 22.4, 21.4. Anal. Calcd for $C_{19}H_{16}NO_4F$: C, 66.86; H, 4.72; N, 4.10; F, 5.57. Found: C, 66.90; H, 4.73; N, 4.08.

1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-methyl-1,4-dihydroquinoline (7c). 1-(*tert*-Butoxycarbonyl)-4-methyl-1,4-dihydropyridine (**5b**) (0.78 g, 3.99 mmol, 1.00 equiv) in THF (30 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (3.99 mL, 1.20 M in cyclohexane, 4.79 mmol, 1.20 equiv) and condensed with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**3a**) (0.79 g, 3.99 mmol, 1.00 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(6,7-diisopropoxy-5-hydroxy-4-methyl-1,4-dihydroquinoline as a white solid (0.70 g, 2.19 mmol, 55%): mp 100−102 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.32$); IR (CH_2Cl_2, KCl, cm^{-1}) 3509 (m), 3056 (m), 1779 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.68 (dd, J = 4.2, 0.9 Hz, 1 H), 5.89 (s, 1 H), 5.21 (dd, J = 4.2, 3.6 Hz, 1 H), 4.89 (sept, J = 6.0 Hz, 1 H), 4.51 (sept, J = 6.0 Hz, 1 H), 3.83−3.75 (m, 1 H), 1.43 (d, J = 6.9 Hz, 3 H), 1.36 (d, J = 6.0 Hz, 6 H), 1.31 (dd, J = 6.0, 1.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.7, 145.0, 134.2, 132.8, 123.8, 122.3, 116.7, 116.5, 101.8, 76.1, 74.5, 27.9, 22.7, 22.6, 22.4, 22.3. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.03; H, 6.51; N, 4.27.

1,8-(Carbonyloxy)-6,7-diethyl-5-hydroxy-4-methyl-1,4-dihydroquinoline (7d). 1-(*tert*-Butoxycarbonyl)-4-methyl-1,4-dihydropyridine (**5b**) (0.59 g, 3.02 mmol, 1.00 equiv) in THF (15 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (2.56 mL, 1.30 M in cyclohexane, 3.33 mmol, 1.10 equiv) and condensed with 3,4-diethyl-3-cyclobutene-1,2-dione (**3b**) (0.42 g, 3.04 mmol, 1.01 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6,7-diethyl-5-hydroxy-4-methyl-1,4-dihydroquinoline as a white solid (0.51 g, 1.97 mmol, 65%): mp 132−133 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.24); IR ($CDCl_3$, KCl, cm^{-1}) 3612 (m), 2973 (s), 2255 (m), 1769 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71 (dd, J = 8.1, 1.8 Hz, 1 H), 5.45 (s, 1 H), 5.22 (dd, J = 8.1, 4.2 Hz, 1 H), 3.86−3.80 (m, 1 H), 2.81−2.63 (m, 4 H), 1.43 (d, J = 6.9 Hz, 3 H), 1.22 (d, J = 7.5 Hz, 3 H), 1.17 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 151.5, 147.9, 134.0, 124.5, 124.1, 123.9, 116.8, 116.7, 107.9, 28.0, 22.6, 19.7, 19.2, 14.8, 14.7. Anal. Calcd for $C_{15}H_{16}NO_3$: C, 69.75; H, 6.24; N, 5.42. Found: C, 69.31; H, 6.63; N, 5.43.

1,8-(Carbonyloxy)-4,6-dimethyl-5-hydroxy-7-isopropoxy-1,4-dihydroquinoline (7e). 1-(*tert*-Butoxycarbonyl)-4-methyl-1,4-dihydropyridine (**5b**) (0.78 g, 3.99 mmol, 1.00 equiv) in THF (25 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (4.36 mL, 1.10 M in cyclohexane, 4.80 mmol, 1.20 equiv) and condensed with 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**3c**) (0.74 g, 4.80 mmol, 1.20 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-4,6-dimethyl-5-hydroxy-7-isopropoxy-1,4-dihydroquinoline as a white solid (0.46 g, 1.67 mmol, 42%): mp 147−148 °C (hexane/diethyl ether); TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.65$); IR (CH_2Cl_2, KCl, cm^{-1}) 3608 (s), 2981 (m), 1771 (s), 1375 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.67 (d, J = 7.2 Hz, 1 H), 5.22 (dd, J = 7.2, 4.2 Hz, 1 H), 4.86 (sept, J = 6.0 Hz, 1 H), 4.65 (br s, 1 H), 3.77−3.74 (m, 1 H), 2.10 (s, 3 H), 1.39 (d, J = 6.9 Hz, 3 H), 1.31 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.9, 148.6, 138.4, 125.1, 124.4, 117.0, 116.5, 110.7, 103.0, 74.1, 27.9, 22.7, 22.6, 9.0. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.19; H, 6.27; N, 5.06.

1,8-(Carbonyloxy)-6-(4-fluorophenyl)-5-hydroxyl-7-isopropoxy-4-methyl-1,4-dihydroquinoline (7f). 1-(*tert*-Butoxycarbonyl)-4-methyl-1,4-dihydropyridine (**5b**) (0.53 g, 2.71 mmol, 1.00 equiv) in THF (15 mL) was metalated −42 °C for 3 h with *sec*-butyllithium (2.30 mL, 1.30 M in cyclohexane, 2.99 mmol, 1.10 equiv) and condensed with 4-(4-flurophenyl)-3-isopropoxy-3-cyclobutene-1,2-dione (**3d**) (0.64 g, 2.73 mmol, 1.01 equiv) in THF (20 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6-(4-fluorophenyl)-5-hydroxyl-7-isopropoxy-4-methyl-1,4-dihydroquinoline as a white solid (0.71 g, 2.00 mmol, 74%): mp 148−149 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.69$); IR (CH_2Cl_2, KCl, cm^{-1}) 3535 (w), 2981 (s), 1789 (m), 1391 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.24 (m, 2 H), 7.16−7.10 (m, 2 H), 6.60 (d, J = 8.1 Hz, 1 H), 5.24 (dd, J = 8.1, 4.2 Hz, 1 H), 5.01 (s, 1 H), 4.71 (sept, J = 6.0 Hz, 1 H), 3.80−3.75 (m, 1 H), 1.40 (d, J = 6.9 Hz, 3 H), 1.11 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.2, 160.9, 150.7, 147.8, 137.9, 133.1, 117.3, 116.5, 116.3, 116.0, 115.3, 102.9, 74.4, 28.2, 22.5, 22.4. Anal. Calcd for $C_{20}H_{17}NO_4F$: C, 67.79; H, 4.84; N, 3.95; F, 5.36. Found: C, 67.55; H, 5.07; N, 3.94.

4-*n*-Butyl-1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-1,4-dihydroquinoline (7g). 1-(*tert*-Butoxycarbonyl)-4-*n*-butyl-1,4-dihydropyridine **5c** (1.07 g, 4.51 mmol, 1.00 equiv) in THF (25 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (4.51 mL, 1.20 M in cyclohexane, 5.41 mmol, 1.20 equiv) and then condensed with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**3a**) (0.89 g, 4.49 mmol, 1.00 equiv) in THF (40 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 4-*n*-butyl-1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-1,4-dihydroquinoline as a white solid (1.05 g, 2.91 mmol, 65%): mp 104−105 °C (diethyl ether/hexane); TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.25$); IR (CH_2Cl_2, KCl, cm^{-1}) 3510 (s), 3060 (w), 2981 (s), 2932 (m), 1777 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.70 (dd, J = 7.2, 1.2 Hz, 1 H), 5.84 (s, 1 H), 5.19 (dd, J = 7.2, 3.9 Hz, 1 H), 4.86 (sept, J = 6.0 Hz, 1 H), 4.47 (sept, J = 6.0 Hz, 1 H), 3.82−3.79 (m, 1 H), 2.01−0.82 (m, 9 H), 1.32 (d, J = 6.0 Hz, 6 H), 1.27 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.8, 144.9, 134.2, 132.7, 123.7, 123.0, 117.6, 114.9, 100.5, 76.1, 74.5, 34.7, 32.8, 27.6, 22.7, 22.6, 22.4, 22.3, 14.0. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.54; H, 7.60; N, 3.94.

4-*n*-Butyl-1,8-(carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-1,4-dihydroquinoline (7h). 1-(*tert*-Butoxycarbonyl)-4-*n*-butyl-1,4-dihydropyridine (**5c**) (0.35 g, 1.47 mmol, 1.00 equiv) in THF (20 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (1.25 mL, 1.30 M in cyclohexane, 1.62 mmol, 1.10 equiv) and then condensed with 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**3c**) (0.23 g, 1.47 mmol, 1.00 equiv) in THF (15 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 4-*n*-butyl-1,8-(carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-1,4-dihydroquinoline as a white solid (0.26 g, 0.82 mmol, 55%): mp 90−91 °C (hexane/diethyl ether); TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.42); IR (CH_2Cl_2, KCl, cm^{-1}) 3595 (w), 2962 (w), 2933 (w), 1777 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, J = 7.2 Hz, 1 H), 5.23 (dd, J = 7.2, 4.2 Hz, 1 H), 5.05 (br s, 1 H), 4.84 (sept, J = 6.0 Hz, 1 H), 3.79 (m, 1 H), 2.10 (s, 3 H), 1.80−1.66 (m, 2 H), 1.30 (d, J = 6.0 Hz, 6 H), 1.25−1.08 (m, 4 H), 0.83 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 151.1, 148.6, 138.4, 125.6, 124.3, 117.5, 111.1, 101.9, 74.1, 35.3, 32.8, 27.6, 22.7, 22.7, 14.0,

9.2. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.72; H, 7.86; N, 3.98.

1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-phenyl-1,4-dihydroquinoline (7i). 1-(*tert*-Butoxycarbonyl)-4-phenyl-1,4-dihydropyridine (**5d**) (0.48 g, 1.87 mmol, 1.00 equiv) in THF (15 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (1.78 mL, 1.10 M in cyclohexane, 1.96 mmol, 1.05 equiv) and then condensed with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**3a**) (0.39 g, 1.97 mmol, 1.05 equiv) in THF (20 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-phenyl-1,4-dihydroquinoline as a white solid (0.43 g, 1.12 mmol, 60%): mp 115−116 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.26); IR (CH_2Cl_2, KCl, cm^{-1}) 3054 (w), 2981 (m), 1781 (s), 1672 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.17 (H), 6.73 (dd, J = 7.2, 1.8 Hz, 1 H), 5.64 (s, 1 H), 5.28 (dd, J = 7.2, 4.2 Hz, 1 H), 4.95−4.87 (m, 2 H), 4.45 (sept, J = 6.0 Hz, 1 H), 1.36 (dd, J = 6.0, 1.2 Hz, 6 H), 1.21 (t, J = 6.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.7, 145.1, 143.6, 134.9, 132.9, 128.5, 126.9, 123.7, 122.5, 116.4, 99.8, 76.1, 74.7, 39.0, 22.7, 22.5, 22.4. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.14; H, 6.10; N, 3.65.

1,8-(Carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-4-phenyl-1,4-dihydroquinoline (7j). 1-(*tert*-Butoxycarbonyl)-4-phenyl-1,4-dihydropyridine (**5d**) (0.89 g, 3.46 mmol, 1.00 equiv) in THF (25 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (3.30 mL, 1.10 M in cyclohexane, 3.63 mmol, 1.05 equiv) and then condensed with 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**3c**) (0.56 g, 3.63 mmol, 1.05 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 45 min), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-4-phenyl-1,4-dihydroquinoline as a white solid (0.48 g, 1.42 mmol, 41%): mp 155−156 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.69); IR (CH_2Cl_2, KCl, cm^{-1}) 3541 (m), 2934 (m), 1773 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.23 (m, 5 H), 6.74 (d, J = 7.2 Hz, 1 H), 5.23 (dd, J = 7.2, 3.6 Hz, 1 H), 4.92−4.88 (m, 2 H), 4.72 (br s, 1 H), 2.02 (s, 3 H), 1.34 (d, J = 4.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.8, 148.7, 143.0, 139.3, 129.3, 128.1, 127.6, 124.9, 124.2, 116.4, 115.0, 112.2, 100.5, 74.2, 39.4, 22.8, 9.2. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.91; H, 5.63; N, 4.11.

1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-(2-methoxyphenyl)-1,4-dihydroquinoline (7k). 1-(*tert*-Butoxycarbonyl)-4-(2-methoxyphenyl)-1,4-dihydropyridine (**5e**) (0.95 g, 3.32 mmol, 1.00 equiv) in THF (30 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (2.81 mL, 1.30 M in cyclohexane, 3.65 mmol, 1.10 equiv) and then condensed with 3,4-diisopropoxy-3-cyclobutene-1,2-dione **3a** (0.79 g, 3.99 mmol, 1.20 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 1 h), and chromatographic purification (Baeckström column, silica gel, 2.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-(2-methoxyphenyl)-1,4-dihydroquinoline as a white solid (0.78 g, 1.90 mmol, 57%): mp 129−130 °C (EtOAc/hexane); TLC (silica gel, 15% EtOAc/hexanes, R_f = 0.25); IR (CH_2Cl_2, KCl, cm^{-1}) 3504 (s), 3062 (s), 2981 (s), 1779 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.18 (m, 1 H), 6.93−6.87 (m, 3 H), 6.72 (d, J = 7.5 Hz, 1 H), 5.83 (s, 1 H), 4.94 (sept, J = 6.0 Hz, 1 H), 4.48 (sept, J = 6.0 Hz, 1 H), 3.89 (s, 3 H), 1.39 (d, J = 6.0 Hz, 6 H), 1.25 (dd, J = 6.0, 2.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.8, 150.8, 145.0, 134.9, 133.0, 131.3, 129.0, 128.0, 123.8, 123.3, 121.1, 116.2, 114.3, 110.7, 99.4, 76.1, 74.6, 55.6, 22.7, 22.5, 22.4. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.24; H, 5.90; N, 3.41.

1,8-(Carbonyloxy)-6,7-diisopropoxy-4-(2-fluorophenyl)-5-hydroxy-1,4-dihydroquinoline (7l). 1-(*tert*-Butoxycarbonyl)-4-(2-fluorophenyl)-1,4-dihydropyridine (**5f**) (0.24 g, 0.87 mmol, 1.00 equiv) in THF (10 mL) was metalated −42 °C for 3 h with *sec*-butyllithium (0.81 mL, 1.30 M in cyclohexane, 1.05 mmol, 1.21 equiv) and then condensed with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (**3a**) (0.21 g, 1.06 mmol, 1.22 equiv) in THF (25 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 1 h), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from 100% hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-6,7-diisopropoxy-4-(2-fluorophenyl)-5-hydroxy-1,4-dihydroquinoline as a white solid (185 mg, 0.46 mmol, 53%): mp 147.2−147.9 °C (EtOAc/hexane); TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.35); IR (CH_2Cl_2, KCl, cm^{-1}) 3504 (s), 3060 (s), 1781 (s), 1389 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22−7.15 (m, 1 H), 7.06−6.70 (m, 3 H), 6.76 (d, J = 7.8 Hz, 1 H), 5.63 (s, 1 H), 5.31−5.27 (m, 2 H), 4.91 (sept, J = 6.0 Hz, 1 H), 4.47 (sept, J = 6.0 Hz, 1 H), 1.37 (d, J = 6.0 Hz, 6 H), 1.20−1.23 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.5, 158.2, 150.6, 145.0, 135.1, 132.8, 130.3, 130.1, 129.9, 128.5, 128.4, 123.6, 123.0, 116.9, 116.9, 115.5, 115.2, 113.3, 98.3, 74.7, 31.9, 31.8, 22.7, 22.4. 22.4. Anal. Calcd for $C_{22}H_{22}NO_5F$: C, 66.16; H, 5.55; N, 3.51; F, 4.76. Found: C, 66.40; H, 5.59; N, 3.44.

1,8-(Carbonyloxy)-4-[4-(*N*,*N*-diallylamino)phenyl]-6,7-diethyl-5-hydroxy-1,4-dihydroquinoline (7m). 1-(*tert*-Butoxycarbonyl)-4-[4-(*N*,*N*-diallylamino)phenyl]-1,4-dihydropyridine (**5b**) (0.45 g, 1.28 mmol, 1.00 equiv) in THF (15 mL) was metalated at −42 °C for 3 h with *sec*-butyllithium (1.08 mL, 1.30 M in cyclohexane, 1.40 mmol, 1.09 equiv) and then condensed with 3,4-diethyl-3-cyclobutene-1,2-dione (**3b**) (0.18 g, 1.30 mmol, 1.02 equiv) in THF (15 mL) at −78 °C. Workup, thermolysis neat (160−165 °C, 1 h), and chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, gradient from hexanes to 50% EtOAc/hexanes) gave 1,8-(carbonyloxy)-4-[4-(*N*,*N*-diallylamino)phenyl]-6,7-diethyl-5-hydroxy-1,4-dihydroquinoline as a white solid (0.33 g, 0.79 mmol, 62%): mp 132−133 °C (EtOAc/hexane); TLC (silica gel, 15% EtOAc/hexanes, R_f = 0.26); IR (CH_2Cl_2, KCl, cm^{-1}) 3514 (m), 2973 (m), 1775 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 8.4 Hz, 2 H), 6.73 (dd, J = 7.8, 1.5 Hz, 1 H), 6.66 (dd, J = 8.4 Hz, 1 H), 5.88−5.76 (m, 2 H), 5.16−5.12 (m, 4 H), 4.77 (br s, 1 H), 4.53 (br s, 1 H), 3.89 (d, J = 5.7 Hz, 4 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.58 (q, J = 7.5 Hz, 2 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.05 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.7. Anal. Calcd for $C_{26}H_{28}N_2O_3$: C, 74.98; H, 6.78; N, 6.73. Found: C, 74.90; H, 6.81; N, 6.77.

Quinoline Quinone Synthesis. 6,7-Diisopropoxy-4-methylquinoline-5,8-dione (8c). 1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-methyl-1,4-dihydroquinoline **(7c)** (194 mg, 0.61 mmol, 1.00 equiv) in 1 mL of acetic acid was treated with *o*-chloranil (329 mg, 1.34 mmol, 2.20 equiv) at room temperature. After 5 h, the reaction mixture was quenched with ice-cold NaOH (20% aqueous) to a pH near 7.0. Ether (100 mL) was added, and the organic layer was washed with water (5 × 25 mL) and then dried ($MgSO_4$) and passed through a pad of neutral alumina. The eluent was concentrated to a red oil that was chromatographed (preparative TLC plate, alumina, 0.25 mm, 50% EtOAc/hexanes) to give 6,7-diisopropoxy-4-methylquinoline-5,8-dione as a yellow oil (96.2 mg, 0.33 mmol, 55%): TLC (silica gel, 50% EtOAc/hexanes, R_f = 0.18); IR (CH_2Cl_2, KCl, cm^{-1}) 3058 (w), 2983 (s), 1667 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (d, J = 4.8 Hz, 1 H), 7.35 (d, J = 4.8 Hz, 1 H), 5.00−4.93 (m, 2 H), 2.76 (s, 3 H), 1.35 (d, J = 3.6 Hz, 6 H), 1.33 (d, J = 3.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 183.5, 181.0, 152.6, 150.1, 148.2, 148.1, 147.1, 76.4, 76.1, 22.7, 22.0; HRMS (EI) calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1313.

4,6-Dimethyl-7-isopropoxyquinoline-5,8-dione (8e). Following the procedure for **8c**, 1,8-(carbonyloxy)-4,6-dimethyl-5-hydroxy-7-isopropoxy-1,4-dihydroquinoline (**7e**) (60 mg, 0.22 mmol, 1.00 equiv) and *o*-chloranil (110 mg, 0.45 mmol, 2.05 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 33% EtOAc/hexanes) 4,6-dimethyl-7-isopropoxyquinoline-5,8-dione as a yellow oil (25 mg, 0.102 mmol, 47%): IR (CH_2Cl_2, KCl, cm^{-1}) 3060 (m), 2986 (m), 1684 (s), 1652 (s), 1621 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, J = 4.8 Hz, 1 H), 7.38 (d, J = 4.8 Hz, 1 H), 5.08 (sept, J = 6.0 Hz, 1 H), 2.80 (s, 3 H), 2.10 (s, 3 H), 1.35 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 187.2, 180.0, 156.3, 152.4, 150.0, 148.4, 133.9, 130.9, 127.2,

53.4, 23.0, 22.2, 9.8; HRMS (EI) calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1047.

4-*n*-Butyl-6,7-diisopropoxyquinoline-5,8-dione (8g). 4-*n*-Butyl-1,8-(carbonyloxy)-6,7-diisopropoxy-5-hydroxy-1,4-dihydroquinoline (**7g**) (330 mg, 0.91 mmol, 1.00 equiv) and *o*-chloranil (494 mg, 2.01 mmol, 2.20 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 50% EtOAc/hexanes) 4-*n*-butyl-6,7-diisopropoxyquinoline-5,8-dione as a red oil (282 mg, 0.85 mmol, 93%): TLC (silica gel, 50% EtOAc/hexanes, R_f = 0.33); IR ($CDCl_3$, KCl, cm^{-1}) 2965 (m), 2935 (m), 2242 (w), 1667 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (d, J = 5.4 Hz, 1 H), 7.37 (d, J = 5.4 Hz, 1 H), 5.02−4.94 (m, 2 H), 3.17 (t, J = 7.5 Hz, 2 H), 1.62−1.39 (m, 4 H), 1.37 (d, J = 6.0 Hz, 6 H), 1.35 (d, J = 6.3 Hz, 6 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 183.2, 180.9, 154.7, 152.5, 148.3, 148.2, 146.8, 129.7, 125.5, 76.3, 76.0, 33.9, 32.2, 22.7, 22.6, 22.6, 13.7; HRMS (EI) calcd for $C_{19}H_{25}NO_4$ 331.1783, found 331.1796.

4-*n*-Butyl-7-isopropoxy-6-methylquinoline-5,8-dione (8h). 4-*n*-Butyl-1,8-(carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-1,4-dihydroquinoline (**7h**) (65 mg, 0.21 mmol, 1.00 equiv) and *o*-chloranil (101 mg, 0.41 mmol, 2.00 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 20% EtOAc/hexanes) 4-*n*-butyl-7-isopropoxy-6-methylquinoline-5,8-dione as a yellow oil (43 mg, 0.15 mmol, 73%): TLC (silica gel, 20% EtOAc/hexanes, R_f = 0.11); IR (CH_2Cl_2, KCl, cm^{-1}) 3058 (m), 2935 (s), 2875 (m), 1685 (s), 1652 (s), 1623 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (d, J = 3.9 Hz, 1 H), 7.34 (d, J = 3.9 Hz, 1 H), 5.04 (q, J = 6.0 Hz, 1 H), 3.14 (t, J = 7.5 Hz, 2 H), 2.05 (s, 3 H), 1.57−1.48 (m, 2 H), 1.46−1.36 (m, 2 H), 1.31 (d, J = Hz, 6 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 186.9, 179.9, 156.1, 154.6, 152.4, 148.7, 133.9, 129.9, 126.7, 34.1, 32.3, 30.3, 23.0, 22.9, 13.9, 9.8; HRMS (EI) calcd for $C_{17}H_{21}NO_3$ 287.1521, found: 287.1516.

6,7-Diisopropoxy-4-phenylquinoline-5,8-dione (8i). 1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-phenyl-1,4-dihydroquinoline (**7i**) (67 mg, 0.18 mmol, 1.00 equiv) and *o*-chloranil (86 mg, 0.35 mmol, 1.99 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25mm, 50% EtOAc/hexanes) 6,7-diisopropoxy-4-phenylquinoline-5,8-dione as a yellow oil (38.7 mg, 0.11 mmol, 62%): TLC (silica gel, 50% EtOAc/hexanes, R_f = 0.47); IR (CH_2Cl_2, KCl, cm^{-1}) 2983 (m), 2250 (m), 1671 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.88 (d, J = 4.8 Hz, 1 H), 7.42−7.38 (m, 4 H), 7.25−7.23 (m, 2 H), 5.02−4.86 (m, 2 H), 1.34 (d, J = 6.0 Hz, 6 H), 1.26 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 181.6, 180.8, 152.8, 152.7, 151.4, 148.2, 147.3, 138.5, 130.1, 128.4, 128.2, 127.8, 76.3, 76.3, 22.8, 22.7; HRMS (EI) calcd for $C_{21}H_{21}NO_4$ 351.1470, found 351.1455.

7-Isopropoxy-6-methyl-4-phenylquinoline-5,8-dione (8j). 1,8-(Carbonyloxy)-5-hydroxy-7-isopropoxy-6-methyl-4-phenyl-1,4-dihydroquinoline (**7j**) (54 mg, 0.16 mmol, 1.00 equiv) and *o*-chloranil (80.7 mg, 0.33 mmol, 2.05 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 50% EtOAc/hexanes) 4-phenyl-6-methyl-7-isopropoxyquinoline-5,8-dione as a yellow oil (40.4 mg, 0.131 mmol, 82%): TLC (alumina, 50% EtOAc/hexanes, R_f = 0.32); IR (CH_2Cl_2, KCl, cm^{-1}) 3058 (m), 2939 (m), 1685 (s), 1657 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, J = 4.8 Hz, 1 H), 7.42−7.36 (m, 4 H), 7.23−7.20 (m, 2 H), 5.08 (sept, J = 6.0 Hz, 1 H), 1.97 (s, 3 H), 1.32 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 185.0, 179.7, 156.4, 152.5, 151.3, 148.5, 138.8, 133.9, 130.2, 128.3, 128.1, 127.7, 126.1, 76.3, 23.1, 15.3; HRMS (EI) calcd for $C_{19}H_{17}NO_3$ 307.1208, found 307.1203.

6,7-Diisopropoxy-4-(2-methoxyphenyl)quinoline-5,8-dione (8k). 1,8-(Carbonyloxy)-6,7-diisopropoxy-5-hydroxy-4-(2-methoxy-phenyl)-1,4-dihydroquinoline (**7k**) (100 mg, 0.24 mmol, 1.00 equiv) and *o*-chloroanil (120 mg, 0.49 mmol, 2.00 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 50% EtOAc/hexanes) 6,7-diisopropoxy-4-(2-methoxyphenyl)quinoline-5,8-dione as a yellow oil (72 mg, 0.19 mmol, 77%): TLC (alumina, 50% EtOAc/hexanes, R_f = 0.23); IR (CH_2Cl_2, KCl, cm^{-1}) 3060 (s), 2983 (m), 1671 (s), 1605 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, J = 4.8 Hz, 1 H), 7.93−7.32 (m, 2 H), 7.11 (dd, J = 7.2, 1.8 Hz, 1 H), 7.01 (t, J = 7.2 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 4.94 (sept, J = 6.4 Hz, 1 H), 4.86 (sept, J = 6.0 Hz, 1 H), 3.62 (s, 3 H), 1.34−1.21 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 181.5, 181.0, 155.6, 153.0, 148.4, 148.4, 147.4, 147.3, 130.1, 130.0, 128.6, 127.9, 126.7, 120.9, 110.5, 76.2, 75.9, 55.3, 22.8, 22.7, 22.6; HRMS (EI) calcd for $C_{22}H_{23}NO_5$ 381.1563, found 381.1576.

6,7-Diisopropoxy-4-(2-fluorophenyl)quinoline-5,8-dione (8l). 1,8-(Carbonyloxy)-6,7-diisopropoxy-4-(2-fluorophenyl)-5-hydroxy-1,4-dihydroquinoline (**7l**) (92 mg, 0.23 mmol, 1.00 equiv) and *o*-chloroanil (102 mg, 0.42 mmol, 1.80 equiv) gave after workup and chromatographic purification (preparative TLC plate, alumina, 0.25 mm, 50% EtOAc/hexanes) 6,7-diisopropoxy-4-(2-fluorophenyl)quinoline-5,8-dione as a yellow oil (70.2 mg, 0.19 mmol, 82%): TLC (silica gel, 50% EtOAc/hexanes, R_f = 0.44); IR (CH_2Cl_2, KCl, cm^{-1}) 3060 (s), 2987 (s), 1671 (m), 1607 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.93 (d, J = 5.1 Hz, 1 H), 7.42−7.40 (m, 2 H), 7.24−7.12 (m, 2 H), 7.00 (t, J = 2.7 Hz, 1 H), 4.96 (sept, J = 6.0 Hz, 1 H), 4.90 (sept, J = 6.0 Hz, 1 H), 1.36 (d, J = 6.0 Hz, 6 H), 1.27 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 181.5, 180.7, 160.6, 157.3, 148.3, 147.7, 147.5, 144.4, 130.7, 130.6, 130.1, 129.2, 126.4, 126.2, 126.0, 124.5, 124.4, 115.5, 115.2, 76.4, 76.3, 22.8, 22.7; HRMS (EI) calcd for $C_{21}H_{20}NO_4F$ 369.1376, found 369.1380.

Construction of the Pyridoacridone Ring System. 1-(2-Bromophenyl)-2,5-dimethylpyrrole (9). A solution of 2-bromoaniline (10.0 g, 58.13 mmol, 1.0 equiv), 2,5-hexanedione (6.848 g, 60 mmol, 1.03 equiv), and AcOH (1.00 mL, 17.47 mmol, 0.30 equiv) in toluene (70 mL) was heated at reflux for 48 h with removal of water. The solution was cooled, diluted with EtOAc (100 mL), washed with 2 M HCl (100 mL), brine (100 mL), 1 M $NaHCO_3$ (100 mL), and brine (100 mL), and dried ($MgSO_4$). After filtration and removal of solvents the resulting brown oil (14.5 g) was purified by chromatography (Baeckström column, silica gel, 2.5 cm × 12 cm, gradient from 100% hexanes to 5% EtOAc/hexanes) or short-path distillation and gave a yellow oil in 97% yield: bp 105 °C (1.7 mmHg); TLC (silica gel, 5% EtOAc/hexanes, R_f = 0.36); IR ($CHCl_3$, KCl, cm^{-1}) 3064 (w), 2991 (m), 2918 (w), 1590 (w), 1483 (s), 1398 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (m, 1 H), 7.44 (m, 1 H), 7.32 (m, 2 H), 5.94 (s, 2 H), 1.97 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.7 (s), 133.5 (d), 130.8 (d), 130.0 (d), 128.5 (s), 128.4 (d), 124.6 (s), 105.9 (d), 12.8 (q). Anal. Calcd for $C_{12}H_{12}BrN$: C, 57.62; H, 4.84; Br, 31.95; N, 5.60. Found: C, 57.77; H, 4.86; N, 5.59.

1-(*tert*-Butoxycarbonyl)-4-[2-(2,5-dimethylpyrrol-1-yl)-phenyl]-1,4-dihydropyridine (11). A solution of 1-(2-bromophenyl)-2,5-dimethylpyrrole (**9**) (5.0 g, 20 mmol, 1.0 equiv) in dry THF (25 mL) was heated at reflux with magnesium turnings (0.535 g, 22 mmol, 1.1 equiv) and iodine (0.02 g, 0.06 mmol) until the magnesium had reacted. The resulting black solution was cooled to room temperature and cannulated into a freshly prepared mixture of pyridine (2.4 mL, 30 mmol, 1.5 equiv), phenyl chloroformate (2.5 mL, 20 mmol, 1.0 equiv), and cuprous iodide (0.19 g, 1.0 mmol, 0.05 equiv) in 100 mL of THF at −23 °C. After 30 min, the reaction mixture was allowed to warm to room temperature and then quenched with NH_4Cl (200 mL) and extracted with EtOAc (100 mL). After removal of solvent, the resulting yellow oil was dissolved in 200 mL of dry toluene, cooled to −78 °C, and treated dropwise with potassium *tert*-butoxide in THF (40 mL, 1.0 M in THF, 40 mmol, 2.0 equiv). After 3 h, the reaction mixture was warmed to room temperature, quenched with water (200 mL), and extracted with EtOAc (100 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Crystallization from methanol gave a white solid (6.03 g, 86%): mp 104−105 °C; TLC (silica gel, 5% EtOAc/hexanes, R_f = 0.24); IR ($CHCl_3$, KCl, cm^{-1}) 3025 (w), 2985 (w), 2924 (w), 1708 (m), 1685 (m), 1488 (w), 1370 (s), 1337 (s), 1320 (s), 1207 (m), 1128 (m), 976 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (m, 1 H), 7.47 (m, 1 H), 7.32 (m, 1 H), 7.13 (m, 1 H), 6.92 (m, 1 H), 6.75 (m, 1 H), 5.92 (s, 2 H), 4.74 (m, 1 H), 4.64 (m, 1 H), 3.71 (m, 1 H), 1.94 (s, 6 H), 1.53 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.0 (s), 144.7 (s), 135.8 (s), 131.1 (d), 129.3 (d), 128.7 (d), 128.5 (s), 127.3 (d), 122.9 (d), 122.7 (d), 108.2 (d), 107.9 (d), 105.8 (d), 82.1 (s), 33.2 (d), 28.2 (q), 12.9 (q). Anal. Calcd

for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.28; H, 7.45; N, 7.92.

1,8-(Carbonyloxy)-6,7-diisopropoxy-4-[2-(2,5-dimethylpyrrol-1-yl)phenyl]-5-hydroxy-1,4-dihydroquinoline (13). 1-(*tert*-Butoxycarbonyl)-4-[2-(2,5-dimethylpyrrol-1-yl)phenyl]-1,4-dihydropyridine (**11**) (3.50 g, 10 mmol, 1.0 equiv) was dissolved in 50 mL of dry THF and cooled to −78 °C. To this solution was added *sec*-butyllithium (9.3 mL, 1.3 M in cyclohexane, 12.02 mmol, 1.2 equiv) dropwise. After 5 h, the solution was cannulated into 3,4-diisopropoxy-3-cyclobutene-1,2-dione (2.376 g, 12.0 mmol, 1.2 equiv) in dry THF (50 mL) at −78 °C. After 2 h, the reaction mixture was quenched with NH_4Cl (100 mL), allowed to warm, and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to a brown oil. From this crude oil, the unreacted dihydropyridine was removed by chromatography (Baeckström column, silica gel, 3.5 cm × 15 cm, 5% EtOAc/hexanes, $R_f = 0.24$; 0.56 g, 16%). The remainder of the chromatographed material was degassed (six cycles, nitrogen−vacuum−nitrogen) and then thermolyzed neat at 160−165 °C for 45 min. Chromatographic purification (Baeckström column, silica gel, 3.5 cm × 15 cm, 10% EtOAc/hexanes) gave a white solid that was recrystallized from methanol (3.128 g, 6.6 mmol, 66%): mp 169−170 °C; TLC (silica gel, 20% EtOAc/hexanes, $R_f = 0.42$); IR ($CHCl_3$, KCl, cm^{-1}) 3508 (br, w), 3025 (w), 2979 (m), 1775 (s), 1384 (m), 1106 (m), 1020 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 2 H), 7.16 (m, 1 H), 6.98 (m, 1 H), 6.56 (dd, $J = 8.1$, 1.7 Hz, 1 H), 5.94 (s, 2 H), 5.69 (br s, 1 H), 4.97 (dd, $J = 8.1$, 4.2 Hz, 1 H), 4.94 (sept, $J = 6.1$ Hz, 1 H), 4.71 (dd, $J = 4.2$, 1.7 Hz, 1 H), 4.50 (sept, $J = 6.2$ Hz, 1 H), 2.12 (s, 3 H), 1.97 (s, 3 H), 1.38 (app t, $J = 6.1$ Hz, 6 H), 1.23 (d, $J = 6.2$ Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.5 (s), 145.0 (s), 141.9 (s), 136.7 (s), 135.0 (s), 132.8 (s), 129.6 (d), 129.4 (d), 129.1 (s), 129.0 (d), 128.1 (s), 127.6 (d), 123.6 (s), 123.5 (s), 116.4 (d), 113.1 (d), 106.4 (d), 106.1 (d), 98.4 (s), 76.1 (d), 74.6 (d), 34.3 (d), 22.8 (q), 22.4 (q), 13.2 (q), 12.6 (q). Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.75; H, 6.40; N, 5.89.

1,8-(Carbonyloxy)-6,7-diisopropoxy-4-(2-aminophenyl)-5-hydroxy-1,4-dihydroquinoline (14). A mixture of protected aniline **13** (2.845 g, 6 mmol, 1.0 equiv), hydroxylamine hydrochloride (8.339 g, 120 mmol, 20.0 equiv), triethylamine (8.363 mL, 60 mmol, 10.0 equiv), and *N*-bromosuccinimide (2.136 g, 12 mmol, 2.0 equiv) in EtOH (80 mL) and water (20 mL) was refluxed for 4 days. After this time, the dark solution was cooled, quenched with 50 mL of water, and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by chromatography (Baeckström column, silica gel, 2 cm × 12 cm, from 20% to 50% EtOAc/hexanes) gave 0.853 g (30%) of starting material and a brown solid that was recrystallized from hexane/E_2O (1.354 g, 3.42 mmol, 57%): mp 111−113 °C; TLC (silica gel, 50% EtOAc/hexanes, $R_f = 0.45$); IR ($CHCl_3$, NaCl, cm^{-1}) 3504 (br, w), 3395 (br, w), 3062 (w), 2981 (m), 2936 (w), 1779 (s), 1684 (m), 1616 (m), 1493 (m), 1481 (m), 1389 (s), 1107 (m), 1026 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03−7.09 (m, 2 H), 6.89 (dd, $J = 8.1$, 1.7 Hz, 1 H), 6.81 (br t, $J = 7.3$ Hz, 1 H), 6.74 (br d, $J = 8.1$ Hz, 1 H), 6.48 (br s, 1 H), 5.28 (dd, $J = 8.1$, 4.1 Hz, 1 H), 5.02 (dd, $J = 4.1$, 1.7 Hz, 1 H), 4.90 (sept, $J = 6.1$ Hz, 1 H), 4.45 (sept, $J = 6.2$ Hz, 1 H), 3.94 (br s, 2 H), 1.37 (d, $J = 6.1$ Hz, 3 H), 1.35 (d, $J = 6.1$ Hz, 3 H), 1.24 (d, $J = 6.2$ Hz, 3 H), 1.23 (d, $J = 6.2$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.6 (s), 145.1 (s), 142.3 (s), 134.9 (s), 133.3 (s), 129.8 (d), 129.6 (s), 127.6 (d), 123.9 (s), 122.0 (s), 120.4 (d), 117.8 (d), 117.3 (d), 113.3 (d), 100.1 (s), 75.8 (d), 74.5 (d), 32.9 (d), 22.6 (q), 22.5 (q), 22.4 (q), 22.2 (q); HRMS (EI) calcd for $C_{22}H_{24}N_2O_5$ 396.1685, found 396.1696. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.75; H, 6.15; N, 7.05.

5,6-Diisopropoxypyrido[2,3,4-*kl*]acridin-4-one (15). A solution of dihydroquinoline **14** (356 mg, 0.9 mmol, 1.0 equiv) in ethanol (5 mL) was treated with *tert*-butyl hydroperoxide (1.0 mL, aqueous solution 70%, 10.43 mmol, 11.59 equiv) and potassium hydroxide (112 mg, 2.0 mmol, 2.22 equiv) for 7 h. The reaction mixture was quenched with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and condensed to a solid residue that was washed with cold Et_2O and recrystallized from hot Et_2O to give a bright yellow solid (207 mg, 0.59 mmol, 66%): mp 174−176 °C; TLC (silica gel, 50% EtOAc/hexanes, $R_f = 0.23$); IR ($CHCl_3$, NaCl, cm^{-1}) 2986 (m), 2935 (w), 1659 (s), 1607 (m), 1574 (m), 1383 (w), 1098 (s), 1005 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.19 (d, $J = 5.5$ Hz, 1 H), 8.52 (br d, $J = 8.1$ Hz, 1 H), 8.50 (d, $J = 5.5$ Hz, 1 H), 8.31 (br d, $J = 8.1$ Hz, 1 H), 7.87 (br t, $J = 8.1$ Hz, 1 H), 7.76 (br t, $J = 8.1$ Hz, 1 H), 5.20 (sept, $J = 6.2$ Hz, 1 H), 4.88 (sept, $J = 6.2$ Hz, 1 H), 1.49 (d, $J = 6.2$ Hz, 6 H), 1.39 (d, $J = 6.2$ Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 181.2 (s), 153.3 (s), 149.9 (d), 149.0 (s), 146.4 (s), 146.3 (s), 145.8 (s), 136.9 (s), 131.9 (d), 131.5 (d), 129.3 (d), 122.8 (d), 121.5 (s), 119.3 (d), 115.8 (s), 77.7 (d), 75.8 (d), 22.9 (q), 22.7 (q); HRMS (EI) calcd for $C_{21}H_{21}N_2O_3$ $(M + H)^+$ 349.1552, found 349.1562. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.13; H, 5.88; N, 8.01.

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Supporting Information Available: ^1H NMR spectra of compounds **5d**−**g**; ^1H and ^{13}C NMR spectra of compounds **8c**,**e**−**l** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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