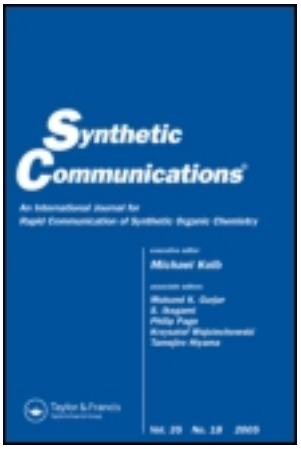

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SYNTHESIS OF 5-SUBSTITUTED AMINOPYRROLO[3,4-b]QUINOLINONES BY A DIORGANOZINC-MEDIATED TANDEM ALKYLATION/CYCLIZATION

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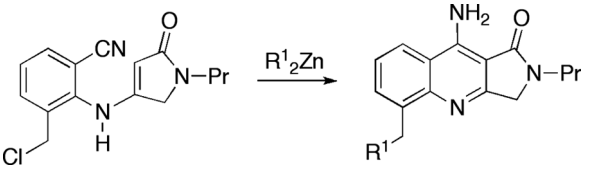
GRAPHICAL ABSTRACT



Abstract *Reaction of diorganozinc reagents with N-(oxopyrrolin-4-yl)-3-chloromethylbenzonitriles provides 5-substituted aminopyrrolo[*3,4-b*]quinolines by an overall single-pot, tandem alkylation/cyclization sequence. Mechanistic considerations suggest an* in situ*–generated* ortho*-quinone methide imine (aza-*ortho*-xylylene) as a reactive intermediate, which may trap an alkyl group from the diorganozinc reagent by a conjugate addition.*

Keywords Aza-*ortho*-xylylene; diorganozinc reagents; *ortho*-quinone methide imine; pyrrolo[*3,4-b*]quinolinones; tandem alkylation/cyclization

INTRODUCTION

As a part of our interest in aminopyrrolo[*3,4-b*]quinolinones **4** and related [b,e]-fused aminopyridines, we wanted access to a range of derivatives with a variety of alkyl and benzyl groups in the 5-position.[1,2] Procedures have been reported for cyclization of N-(oxopyrrolin-4-yl)-3-substituted benzonitriles (enaminones **3**) to provide 5-substituted quinolines **4**, which were in turn derived from condensation of anthranilonitriles **1** with cyclic 1,3-diones, such as the tetramic acid **2**[3,4] (Scheme 1). Introducing substituents at the 5-position of the quinoline ring, by the sequence outlined in Scheme 1, requires 3-substituted anthranilonitriles **1** as reactants. In fact, general methods to prepare 3-substituted anthranilonitriles have been reported, which were used to access a number of quinoline derivatives.[5,6] However, a more versatile synthetic approach to **4** would be advantageous. A particularly

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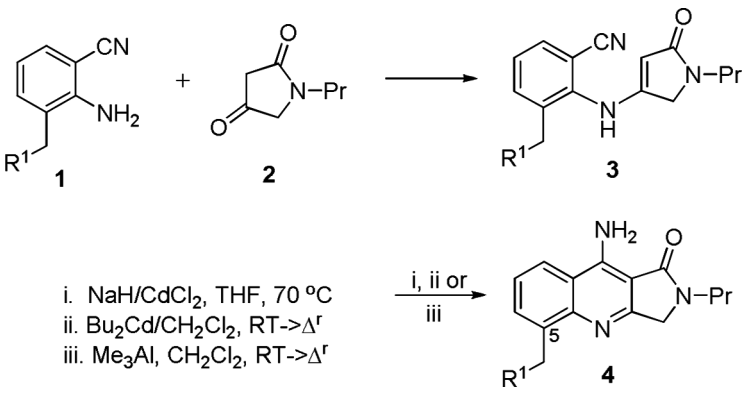
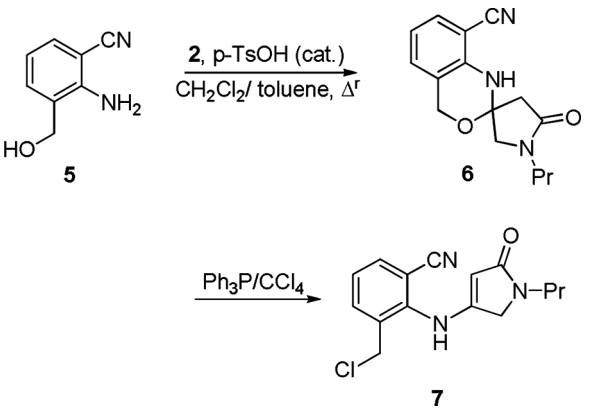


Scheme 1. Cyclization of enaminones derived from 2-aminobenzonitriles condensed with cyclic 1,3-diones to produce quinolones.

attractive approach was envisioned through the intermediacy of a substituted quinoline derivative of **4**, or an immediate precursor, that would permit the late-stage introduction of alkyl and benzyl groups in the 5-position. We report herein our success in developing a synthetic approach to quinoline **4** with introduction of the R^1 substituent in the penultimate step. Furthermore, mechanistic considerations in our procedure suggest the formation of an in situ–generated *ortho*-quinone methide imine. *Ortho*-quinone methide imines have been alternatively referred to in the literature as: aza-*ortho*-xylylenes and *ortho*-iminoquinodimethanes. Such reactive intermediates have found extensive utility in the construction of a variety of heterocycles, primarily through cycloaddition or electrocyclization reactions.[7] The highly reactive *ortho*-quinone methide imine traps an alkyl group from the diorganozinc reagent by a conjugate-type addition. This provides a key intermediate, which cyclizes to form the desired substituted quinoline derivative **4** by a one-pot, tandem deprotonation/addition/cyclization sequence.

RESULTS AND DISCUSSION

As a general approach to synthesizing 5-substituted quinolines **4**, we proposed exploiting 3-(hydroxymethyl)anthranilonitrile **5** as a synthetic precursor that could provide an intermediate that would allow further, late-stage elaboration. Initially, we planned to selectively protect the hydroxyl group of **5**, condense **5** with tetramic acid **2**, and then cyclize it using one of our previously described protocols.[3,4] Removal of the protecting group would then allow further derivatization, such as conversion of the hydroxy to a suitable leaving group and displacement with carbon nucleophiles. Effectively, this would allow incorporation of a variety of alkyl side chains in the last step of the synthesis. Unfortunately, we were not able to cleanly protect the hydroxy group of **5** without also masking the aniline nitrogen. However, we did find that heating together **5** with N-propyltetramic acid **2** in the presence of catalytic *p*-toluenesulfonic acid with azeotropic removal of water provided spirohemiaminal **6**, in excellent yield, instead of the anticipated enaminone **3** ($R^1 = OH$) (Scheme 1).

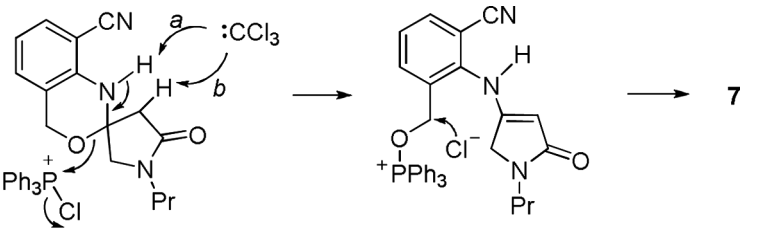


Scheme 2. Formation of chloromethyl-substituted enaminone **7**.

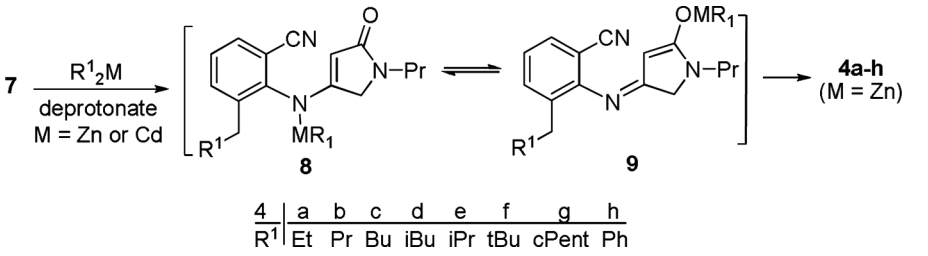
Subsequent exposure of **6** to Ph_3P/CCl_4 induced a ring cleavage of the oxazine ring, which resulted in net replacement of hydroxyl with chloride to afford **7**. The use of Ph_3P/CCl_4, which generates chlorotriphenylphosphonium trichloromethide, likely induces ring opening of in **6** via the weakly basic trichloromethide with incorporation of chloride via the oxyphosphonium salt[8] (Scheme 3).

The fragmentation may occur by one of two pathways. Path a would induce β-elimination through deprotonation of the aniline nitrogen N-H, and path b would induce elimination through one of the hydrogens α to the lactam carbonyl (arrows not shown). Molecular modeling on an energy-minimized structure suggests a dihedral angle of ~174° for pathway a. This positions the labile aniline hydrogen in a nearly ideal *anti* orientation to the fragmenting bond. By comparison, the two hydrogens α to the carbonyl group of the lactam are in less favorable orientations to induce ring cleavage (dihedral angles nearly eclipsed, <5°, and gauche, ~105°). Subsequent attack of chloride on the intermediate oxyphosphonium salts provides **7**.

We next focused our attention on inducing cyclization of enaminone **7** to produce quinoline **4** (R^1=Cl) as an advanced synthetic intermediate. Thus, exposure of **7** to 1.1 eq of NaH followed by the addition of $CdCl_2$ according to the published procedure, failed to provide any identifiable products.[3] Furthermore, an alternative procedure using trimethylaluminum also failed to provide the desired tricycle.[4] We expected that **7**, as a benzylic halide, should be reactive toward nucleophilic displacement of the chloride using suitable, relatively nonbasic organometallic reagents.[9]



Scheme 3. Proposed mechanism for formation of enaminone **7**.



Scheme 4. Diorganozinc or -cadmium induced alkylation/cyclization of enaminone **7**.

This would incorporate, in a penultimate step, an R^1 substituent into the enaminone **3** in a position that would become the eventual 5-position side chain on **4** after cyclization. Diorganocadmium reagents have also been demonstrated to promote the cyclization of enaminones **3** to the tricyclic rings **4**. Thus, we explored the possibility that diorganocadmium reagents might be able to promote alkylation of **7** and cyclization to **4** in one pot (Scheme 4).

To investigate this approach, **7** was reacted with freshly distilled dibutylcadmium, at 0 °C in dichloromethane, followed by warming to ambient temperature. Analysis of aliquots taken from the reaction (aqueous ammonium chloride quench) at selected time intervals revealed the formation of a complex mixture of products, along with complete consumption of the starting chloride **7**. Only a trace of the desired product **4** (R^1 = butyl) was detected. Several additional attempts to promote the reaction by variations of the reaction conditions, such maintaining the temperature at, or even below, 0 °C did not improve the results. The more reactive diorganozinc reagents were next evaluated because of the failure of the organocadmium reagents promote the reaction. Distilled dibutylzinc was reacted with **7** at 0 °C in dichloromethane for 30 min. Quenching the reaction mixture at this point afforded the substituted enaminone **3** (R^1 = butyl) in 89% yield. The reaction of **7** with dibutylzinc was then repeated. However, instead of quenching at 0 °C, the reaction was allowed to warm to ambient temperature and then was heated to ~45 °C (i.e., gentle reflux). After heating at reflux for 8 h the reaction was quenched, and **4c** was isolated in a 66% yield in a one-pot alkylation/cyclization. The procedure was readily extended to the synthesis of other substituted quinolines **4** (Table 1).

The facile nature of the alkylation reaction suggests an 1,4-elimination of the chloride from **7**, perhaps induced by deprotonation of the acidic enaminone NH proton by the diorganozinc reagent as suggested by intermediate **10** (Scheme 5). The resulting highly reactive *ortho*-quinonone methide imine **11** would then be positioned for a rapid conjugate addition of the diorganozinc reagent, restoring the benzo ring aromaticity to provide **8** or tautomer **9** (Scheme 4, M = ZnR^1; see Ref. 10). Subsequent cyclization from these intermediates, as described previously, would form the quinoline ring system.[3,4]

This single-pot alkylation/cyclization sequence provides a convenient method to assemble 5-substituted quinoline derivatives from a late-stage common intermediate. Mechanistically, the intermediacy of a highly reactive *ortho*-quinone methide imine is suggested, which can provide the drive for the unique deprotonation/intramolecular alkylation/cyclization sequence we have described. Thus, reported

Table 1. 5-Substituted aminopyrrolo[*3,4-b*]quinolines **4**: Yields and selected characterization data

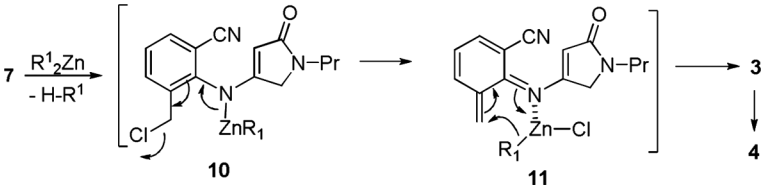
4	R^1	Yield[a] (%)	Mp[b]	^{1}H NMR (δ, *J* = Hz)[c]	MS[d]	IR ($CBrCl_3$, cm^{-1})	Elemental analysis
a	Et	66	159–160	0.89 (t, 3H, *J* = 7.0), 0.92 (t, 3H, *J* = 7.3), 1.66 (m, 4H), 3.08 (t, *J* = 7.4, 2H), 3.45 (t, *J* = 7.0, 2H), 4.42 (s, 2H), 7.36 (dd, *J* = 7.0, *J* = 8.4, 1H), 7.55 (d, *J* = 7.0, 1H), 8.17 (d, *J* = 8.4, 1H)	284	3355, 2960, 1675, 1635, 1605, 1455, 1195	Calcd. for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83 Found: C, 72.15; H, 7.54; N, 14.27
b	Pr	41	126–126.5	0.95 (t, 3H, *J* = 7.2), 0.97 (t, 3H, *J* = 7.3), 1.42 (m, 2H), 1.72 (m, 4H), 3.22 (t, *J* = 7.8, 2H), 3.58 (t, *J* = 7.2, 2H), 4.43 (s, 2H), 6.36 (bs, 2H),7.38 (dd, *J* = 7.2, *J* = 8.3, 1H), 7.56 (d, *J* = 7.2, 1H), 7.69 (d, *J* = 8.3, 1H)	293	3360, 3165, 1685, 1635, 1205	Calcd. for $C_{18}H_{23}N_3O$: C,72.69; H, 7.79; N, 14.13 Found: C, 72.79; H, 7.69; N, 14.12
c	Bu	66	141.5–143	0.90 (t, *J* = 7.0, 3H), 0.99 (t, *J* = 7.4, 3H), 1.40 (m, 4H), 1.73 (m, 4H), 3.21 (t, *J* = 7.5, 2H), 3.58 (t, *J* = 7.1, 2H), 4.43 (s, 2H), 6.38 (bs, 2H),7.38 (dd, *J* = 7.2, *J* = 8.3, 1H), 7.57 (d, *J* = 7.2, 1H), 7.69 (d, *J* = 8.3, 1H)	312	3390, 3120, 2955, 1675, 1605, 1200	Calcd. for $C_{19}H_{25}N_3O$: C, 73.29; H, 8.09; N, 13.49 Found: C, 73.52; H, 8.12; N, 13.60
d	iBu	49	125–128	0.97 (d, *J* = 6.0, 6H), 0.99 (t, *J* = 7.3, 3H), 1.62-1.76 (m, 5H), 3.23 (t, *J* = 7.5, 2H), 3.58 (t, *J* = 7.0, 2H), 4.43 (s, 2H), 6.30 (bs, 2H),7.38 (dd, *J* = 7.0, *J* = 8.3, 1H), 7.57 (d, *J* = 7.0, 1H), 7.67 (d, *J* = 8.3, 1H)	312	3190, 2955, 1681, 1635, 1605, 1200	Calcd. for $C_{19}H_{25}N_3O$: C, 73.29; H, 8.09; N, 13.49 Found: C, 72.96; H, 8.08; N, 13.33

(*Continued*)

Table 1. Continued

4	R^1	Yield[a] (%)	Mp[b]	^{1}H NMR (δ, J = Hz)[c]	MS[d]	IR ($CBrCl_3$, cm^{-1})	Elemental analysis
e	iPr	35	154–155	0.93 (d, J = 6.7, 6H), 0.99 (t, J = 7.0, 3H),), 1.62 (m, 2H), 1.70 (m, 1H), 3.07 (d, J = 7.2, 2H), 3.58 (t, J = 7.1, 2H), 4.42 (s, 2H), 6.33 (bs, 2H),7.38 (dd, J = 7.0, J = 8.2, 1H), 7.54 (d, J = 7.0, 1H), 7.67 (d, J = 8.2, 1H)	298	3400, 3190, 2945, 1675, 1635, 1605, 1455, 1215, 1200	Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.13 Found: C, 72.67; H, 7.71; N, 14.17
f	tBu	65	175–177	0.93 (s, 9H), 1.00 (t, J = 7.3, 3H),), 1.70 (m, 4H), 3.23 (s, 2H), 3.58 (t, J = 7.2, 2H), 4.40 (s, 2H), 6.31 (bs, 2H),7.39 (dd, J = 6.9, J = 8.1, 1H), 7.56 (d, J = 6.9, 1H), 7.69 (d, J = 8.1, 1H)	312	3385, 3155, 2950, 1675, 1635, 1605, 1460, 1220	Calcd. for $C_{19}H_{25}N_3O$: C, 73.29; H, 8.09; N, 13.49 Found: C, 73.27; H, 8.10; N, 13.46
g	cPent	51	160–160.5	0.99 (t, J = 7.3, 3H),), 1.29 (m, 2H), 1.51 (m, 2H), 1.87 (m, 2H), 2.35 (m, 1H), 3.21 (d, J = 7.5, 2H), 3.58 (t, J = 7.1, 2H), 4.43 (s, 2H), 6.33 (bs, 2H),7.37 (dd, J = 7.0, J = 8.3, 1H), 7.57 (d, J = 7.0, 1H), 7.68 (d, J = 8.3, 1H)	324	3395, 3050, 1675, 1605	Calcd. for $C_{20}H_{25}N_3O$: C, 72.27; H, 7.79; N, 12.99 Found: C, 73.84; H, 7.73; N, 12.88
h	Ph	23	219–220.5	0.89 (t, J = 7.2, 3H), 1.64 (m, 2H), 3.46 (s, 2H), 3.46 (t, J = 7.3, 2H), 4.44 (s, 2H), 4.50 (s, 2H), 7.14-7.50 (m, 7H), 7.55 (bs, 2H), 8.20 (d, J = 8.3, 1H)	332	3395, 2970, 1675, 1635, 1605, 1460, 1200	Calcd. for $C_{21}H_{21}N_3O$: C,76.11; H,6.39; N,12.68 Found: C,75.81; H,6.64; N,12.22

[a]Yields are isolated, recrystallized products.
[b]Melting points are uncorrected (°C).
[c]Spectra recorded in $CDCl_3$ except for **4a** and **4h**, which were recorded in DMSO-d_6.
[d]Methane DCI, $M^+ + 1$.



Scheme 5. Proposed intermediacy of ortho-quinone methide imines in the tandem alkylation/cyclization of **7** with diorganozinc reagents.

addition of carbon nucleophiles to *ortho*-quinone methide imines, as we are suggesting in Scheme 5 (through intermediate **11**) are exceedingly rare.[11] We believe this methodology should be readily extendable to the construction of other [*b,e*]annulated pyridine derivatives through the intermediacy of appropriately substituted α-chloromethylanilinoenamines as precursors to highly reactive *ortho*-quinone methide imines. The known convenient preparation of functionalized diorganozinc reagents further extends the potential utility of this single-pot alkylation/cyclization sequence to construct highly elaborated heterocyclic derivatives.[12]

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Thin-layer chromatography (TLC) analyses were performed on silica gel GHLF. Flash chromatography refers to the method reported by Still. All reactions were performed under an argon atmosphere using standard techniques for manipulation of air- and moisture-sensitive reagents.[13] Ambient temperature refers to 23 °C (±3 °C). Melting points were taken on a capillary apparatus. ^{1}H NMR spectra were obtained at either 250 or 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Chemical ionization mass spectrometry (methane ionization gas) was obtained on a mass spectrometer operating at a source pressure of >1 Torr. Analytical data for compounds **4a–h** is given in Table 1.

Preparation of 4-Cyanobenz[d]-l,3-oxazine-2-spiro-4′-(1′-propyl)-2′-pyrrolidinone 6

3-Ethoxycarbonyl-1-propyl-2,4-dioxopyrrolidine (**3**) (21.3 g, 100 mmol) was heated to reflux in slightly moist acetonitrile (3.5 L) for 1.5 h. The volatiles were removed using an aspirator vacuum to afford 1-propyl-2,4-dioxopyrrolidine **2** as a viscous oil. A mixture of freshly prepared **2**, 2-amino-3-(hydroxymethyl)benzonitrile (9.87 g, 66.6 mmol), and *p*-TsOH (0.64 g, 3.33 mmol) in toluene (50 mL) and CH_2Cl_2 (50 mL) was heated to gentle reflux.[14] The reaction mixture was mounted on a Dean–Stark trap to remove water as an azeotrope with toluene and CH_2Cl_2. Heating was continued until about 50 mL of solvent had been collected. An additional portion of CH_2Cl_2 (75 mL) was added. Heating was again continued with collection of a second 50-mL fraction of solvent. The reaction was cooled to ambient temperature. Saturated aqueous $NaHCO_3$ and ethyl acetate were added, and the mixture was

partitioned between the layers. The layers were separated and the aqueous phase was extracted with an additional portion of ethyl acetate. The combined organic extracts were washed with water and then brine. After drying ($MgS0_4$) and concentrating, the crude product was purified by flash chromatography on silica gel using ethyl acetate–hexanes (2:3) as the eluent. The product was obtained as a viscous oil, which solidified upon standing (17.4 g, 64 mmol, 96%); TLC, Rf = 0.17, ethyl acetate–hexanes (1:1); ^{1}H NMR: (DMSO-d_6) 0.83 (t, $J = 7.2$ Hz, 3H), 1.47 (m, 2H), 2.57 (d, $J = 16.8$ Hz, 1H), 2.76 (d, $J = 16.8$ Hz, 1H), 3.19 (m, 2H), 3.35 (s, 2H), 4.83 (s, 2H), 6.76 (dd, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 11.1, 20.4, 44.1, 43.8, 58.2, 61.9, 85.0, 96.6, 118.1, 118.6, 119.5, 129.2, 131.5, 142.7, 170.2; MS 272 ($m^+ + 1$); IR ($CBrCl_3$, cm^{-1}): 3350, 2970, 2230, 1685, 1603, 1505, 1315, 1145.

Preparation of 2-(1-Propyl-2-oxo-3-pyrrolin-4-yl)amino-3-(chloromethyl)benzonitrile 7

A sample of **6** (6.31 g, 23.3 mmol) was mixed with triphenylphosphine (6.69 g, 25.5 mmol) and CCl_4 (22.5 mL, 233 mmol) in CH_2Cl_2 (50 mL). After stirring overnight (about 15 h), an additional portion of triphenylphosphine (1.83 g, 6.98 mmol) was added, and the mixture was stirred for 4 h. The volatiles were removed, and the residue was partitioned between ethyl acetate and water. The layers were separated, and the aqueous phase was extracted using additional ethyl acetate. The combined organic layer was washed with brine, dried, and concentrated. The residual oil was dissolved in CH_2Cl_2:hexanes (1:1, 60 mL). The solution was scratched with a glass rod until crystallization was induced. After setting for several hours, the product **7** was filtered off using chilled CH_2Cl_2–hexanes (1:1) as a wash solvent. The filtrate was concentrated, and the resulting solid residue (mostly triphenylphosphine oxide) was recrystallized from *tert*-butylmethylether. After filtering off the triphenylphosphine oxide, the remaining filtrate was concentrated and then recrystallized from CH_2Cl_2–hexanes (1:1) to obtain an additional crop of **7**. The combined crops afforded 4.21 g (14.5 mmol, 62%) of a white solid: mp 170–172.5 °C; TLC, Rf = 0.12, ether; ^{1}H NMR (DMSO-d_6): 0.83 (t, $J = 7.2$ Hz, 3H), 1.50 (m, 2H), 3.22 (t, $J = 6.9$ Hz, 2 H), 4.06 (s, 2H), 4.33 (s, 1H), 4.80 (s, 2H), 7.51 (m, 1H), 7.89 (m, 2H), 9.01 (s, 1H).

Reaction of Diorganozinc Reagents with Enaminone 7 to Produce 4

A mixture of **7** (1.0 g, 3.45 mmol) and $ZnBr_2$ (0.16 g, 0.71 mmol, dried under high vacuum for 1 h at 180 °C) was dissolved in CH_2Cl_2 (5.0 mL) under an argon atmosphere. The mixture was cooled in an ice bath and treated with the diorganozinc reagent (10.35 mmol, 3 equivalents), either neat or as a solution in CH_2CI_2. Following the addition of the diorganozinc reagent, the mixture was warmed to ambient temperature and stirred for 1 h. The mixture was then heated to reflux (bath temperature ~45 °C) and stirred for 8–24 h. The mixture was cooled to ambient temperature and quenched by pouring slowly into excess cold aqueous NH_4Cl. After stirring for several minutes, ethyl acetate was added, and the layers separated. The aqueous phase was extracted with additional ethyl acetate, and the combined organic layer washed

with brine. After drying ($MgSO_4$), the extracts were concentrated to leave the crude product **4**. The crude material was generally purified by flash chromatography using mixtures of ethyl acetate and hexanes as the eluent. Chromatographed products were recrystallized from *tert*-butylmethylether or mixtures of *tert*-butylmethylether and hexanes. Full characterization data for all quinolines **4** are listed in Table 1.

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