Palladium(0)-Catalyzed Syntheses of Indoloquinones

Louis S. Hegedus,* Thomas A. Mulhern, and Atsunori Mori

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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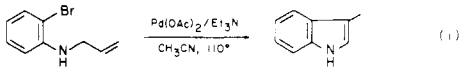
Synthetic approaches to 2-bromo-3,6-diamino-5-methyl-1,4-benzoquinones, hydroquinones, and their corresponding acetates are described. Palladium(0)-catalyzed cyclization of their *N*-allyl derivatives to indoloquinones has been developed.

As part of an overall program to develop organometallic approaches to the indoloquinone nucleus common to the mitosenes[1] we developed a palladium(0)-catalyzed cyclization of *N*-allyl-2-bromoanilines to indoles (eq 1).[2] This

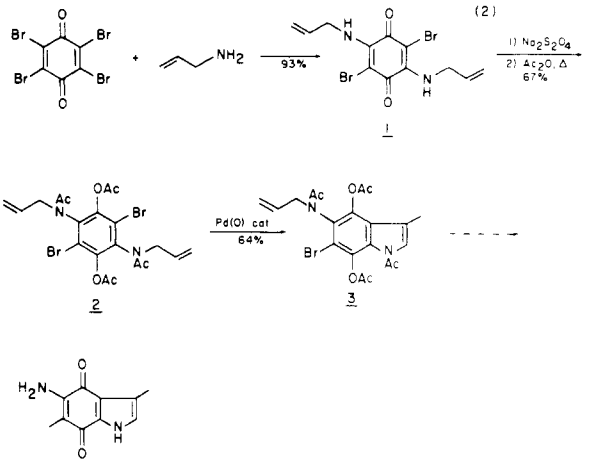


(1)

procedure was efficient for the synthesis of a number of simple indoles. For the synthesis of the desired indoloquinone systems, appropriately constituted *N*-allylbromoquinones were required, as was an assessment of the efficiency of the palladium(0)-catalyzed cyclization with highly substituted bromoquinone substrates. In this paper both of these problems are addressed.

Results and Discussion

A rapid entry into the desired bromoquinone substrates is shown in eq 2. Amination of bromanil with excess allylamine produced the desired 2,5-dibromo-3,6-diaminobenzoquinone **1** in excellent yield. Reduction and acetoxylation led to the fully protected dibromohydroquinone **2**, which underwent palladium(0)-catalyzed cyclization to produce indole **3** in good yield. Cyclization of the free quinone **1** was not attempted since oxidation of the palladium(0) catalyst was feared. Protection of the hydroquinone **2** as the di-*O*-methyl species was attempted, but this substrate failed to undergo the cyclization reaction, as did the unprotected hydroquinone **2** itself. This is not surprising, since electron-rich aromatics are relatively unreactive to oxidative addition reactions. Although an *O*-bromo-*N*-allyl moiety remained in compound **3**, a second cyclization to give the bis(indole) was not observed, indicating that replacement of the first, electron-withdrawing bromo group by the relatively electron-rich indole ring deactivated the system to further oxidative addition reactions.



(2)

Compound **3** is the A–B ring system of the mitosenes in protected form. Replacement of the remaining bromine by a methyl group followed by deprotection and oxidation would give the desired indoloquinone. However, attempted methylation of **3** proved unsuccessful. The presence of several reactive acetyl groups precluded approaches involving direct lithiation, as evidenced by the decomposition of **3** by *t*-BuLi/MeI at −120 °C. Uncyclized substrate **2** was also decomposed by this (and several other) lithiation/alkylation procedures. Compound **3** was also resistant to methylation by both MeCu and Me_2CuLi. Under standard reaction conditions[3] no reaction resulted, while forcing conditions resulted in decomposition of the substrate.

In light of these problems, it was decided to have the methyl group present in the starting quinone, prior to any elaboration. Commercially available 2-methyl-1,4-benzoquinone (toluquinone) was an attractive starting material. However, because each ring position is unique in this compound (in contrast to benzoquinone itself) *regio*specific introduction of the bromide at C_5 and amino groups at C_6 and C_3 was required.

Amination of 1,4-benzoquinones[4] may occur by either addition or substitution pathways. With addition, the benzoquinone undergoes 1,4-addition of the amine in a Michael fashion to give a hydroquinone intermediate. Reoxidation of the hydroquinone by air, by chemical oxidants, or by the benzoquinone starting material affords the aminated benzoquinone. Repetition of this sequence with additional amine affords diaminoquinone adducts. There is a very strong preference for the 1,4-orientation of amine substituents in diaminoquinones.

Amination of benzoquinones by substitution results in replacement of a labile substituent by nitrogen. Unlike addition, the substitution sequence affords aminated products in the quinone oxidation state. Sequential substitution at the quinone ring can occur to give polyaminated benzoquinones. As before, diaminoquinones formed by this method show a marked preference for a 1,4-orientation on the quinone ring.

The regioselective amination of unsymmetrically substituted 1,4-benzoquinones has been studied extensively but is not completely understood. Regioselectivity is determined by complex electronic and steric factors imparted

(1) Takahashi, K.; Kametani, T. *Heterocycles* **1978**, *9*, 293; **1979**, *13*, 411.

(2) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709.

(3) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1. Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980.

(4) (a) Finley, K. T. In "The Chemistry of Quinoid Compounds"; Patai, S., Ed.; Wiley: New York, 1974; part 2, pp 877–1144. (b) Ulrich, H.; Richter, R. In "Methoden der Organische Chemie (Houben-Weyl)"; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. VII/3a, part 1, pp 385–596.

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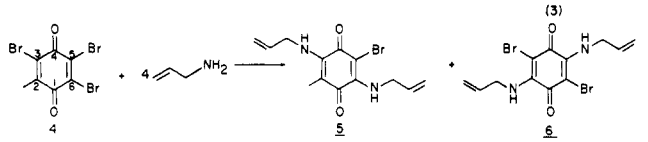
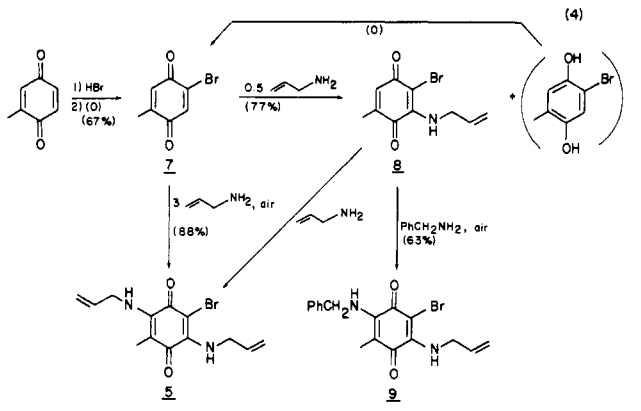
to the ring by the substituents. Several general trends are apparent. First, amination occurs predominantly at the most electrophilic site on the quinone ring. This is true for both substitution and addition pathways and is determined largely by the substituents already present on the ring. For example, amination adjacent to an electron-donating substituent such as a methoxy or an amino group is unfavorable. Conversely, amination adjacent to an electron-withdrawing group such as a bromine substituent is favored. Second, in the absence of overriding electronic differences, addition is preferred over substitution presumably for steric reasons. Third, within the confines of substitution, the relative preference for functional group displacement is roughly MeO > Br, Cl > Me. Finally, there is a strong tendency for 1,4-orientation of amine substituents in diaminoquinones. This is true for both the diamination of benzoquinones and for the amination of monoaminoquinones. Thus, the regiochemistry of diaminoquinones is determined by the site of the first amination since any subsequent amination will occur so as to give a 1,4-diaminoquinone product.

Both substitution and addition approaches to the requisite 2-bromo-3,6-diamino-5-methyl-1,4-benzoquinone were attempted. Treatment of tribromotoluquinone **4** (from bromination of methyl benzoquinone) with excess allylamine gave a mixture of the desired monobromoquinone **5** and the undesired dibromoquinone **6**, resulting from the unusual (but precedented)[5] displacement of the methyl group (eq 3). This lack of specificity is likely the



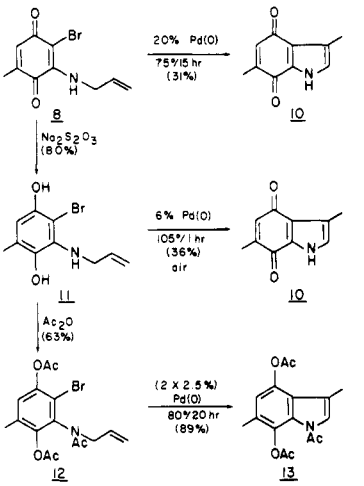
result of nonselective initial amination at both C_5 and C_6. Introduction of the second amine group para to the first would give the observed mixture of products.

Since the substitution approach to **5** was unselective, a strategy based on amine addition to monobromotoluquinone **7** was developed (eq 4). Treatment of **7** with 0.5 equiv of allylamine resulted in exclusive amination α to

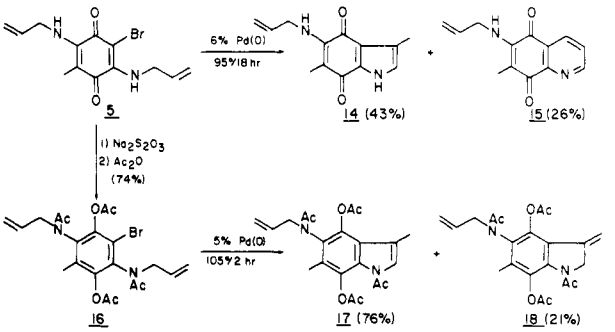


the halogen, giving the desired quinone **8** in good yield. Under these conditions, starting quinone **7** served as an oxidant for the initially produced aminohydroquinone. It was recovered by aerial oxidation and recycled. When excess allyl amine was used, diamination resulted, giving exclusively the desired diaminoquinone **5**. Monoaminoquinone **8** also underwent clean amination by benzyl amine to give diaminoquinone **9**, in which the two amino groups were differentiated. This approach provided ready access

Scheme I



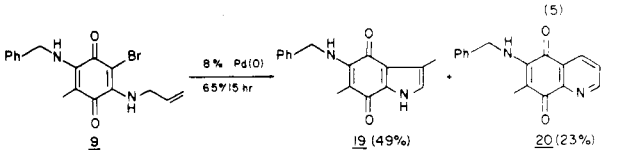
Scheme II



to the aminoquinones required for cyclization studies.

Although palladium(0)-catalyzed oxidative addition/insertion ("Heck") reactions have been extensively studied,[6] little is known about the behavior of quinonoid substrates. Thus, detailed cyclization studies of **5**, **8**, and **9** were carried out. The same general conditions [$Pd(OAc)_2/Et_3N(o\text{-}tol_3P/CH_3CN$] were used in all cases, but the temperature and catalyst amounts were altered in an attempt to optimize the yield. The results with monoaminoquinone **8** are summarized in Scheme I. Both quinone **8** and hydroquinone **11** underwent cyclization only in low yield, despite attempts to optimized this process. This low yield reflects both the relative instability of the quinone precursor and products to the somewhat severe reaction conditions and the low reactivity of electron-rich halides toward Heck-type processes. In contrast, the fully acetylated hydroquinone **12**, being both more stable and more electron deficient than either **8** or **10**, underwent clean cyclization in high yield to give the fully acetylated indolohydroquinone **13**.

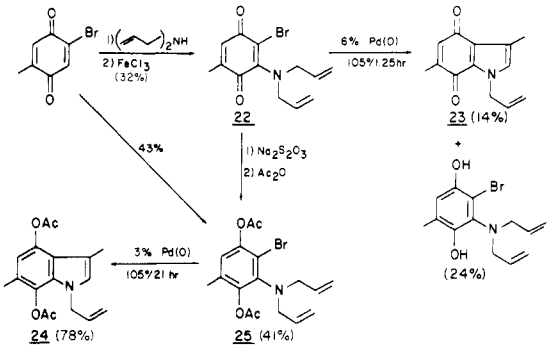
Diaminoquinone **5** behaved somewhat differently (Scheme II). Cyclization of the *free* quinone led to mixtures of the desired indoloquinone **14** and the unexpected quinoline **15**, resulting from alkylation of the *terminal* carbon of the *N*-allyl group. This change in regiochemistry was also observed with diaminoquinone **9**, which cyclized to give both indole and quinoline products (eq 5). These



(5) Reference 4a, pp 1079–1083.

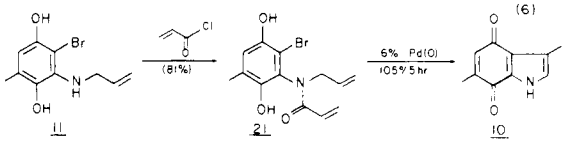
(6) Heck, R. F. *Org. React.* (*N.Y.*) **1982**, *27*, 245.

Scheme III



results clearly demonstrate the sensitivity of the regiochemistry of cyclization to the remote substitution on the quinone ring. Reduction and acetylation of quinone **5** followed by cyclization produced excellent yields of indole **17** and its exocyclic isomer **18**. (Compound **18** is the *primary* β-hydride elimination product,[2] which must subsequently rearrange to **17** by a readdition–β-elimination process. The amount of **18** obtained was dependent on reaction time, with longer reaction times giving relatively more of **17** but lower overall yields.)

The palladium(0)-catalyzed cyclization of fully acetylated aminohydroquinones thus provided an efficient entry into the aminoindoloquinone ring systems found in the synmitosenes. Methods for employing this approach to synthesize the complete tricyclic pyrroloindoloquinone ring system found in the mitosenes were then explored. The most direct way to do this is to incorporate the elements of the C ring into the initial aminoquinone starting material. Accordingly, hydroquinone **11** was N-acylated with acryloyl chloride to produce *N*-allyl-*N*-acryloylhydroquinone **21** (eq 6). Palladium(0)-catalyzed cyclization of



this material resulted in deacylation as well as cyclization and only indoloquinone **10** was isolated. Loss of the acryloyl group occurred after cyclization, since deacetylated starting material was never detected, even when the reaction was run to only 50% conversion. This is reasonable, since indolic amides are considerably less robust than other amides.[7]

To circumvent this problem, *N,N*-diallylaminoquinone **22** was synthesized by procedures developed above (Scheme III). Amination occurred exclusively α to the bromine, as expected, and diamination did not occur even in the presence of excess dialkylamine.[8] Attempts to aminate **22** at the remaining unsubstituted position with either allyl- or benzylamine failed. Instead, the diallylamino group was displaced, and bis(allylamino)quinone **5** or bis(benzylamino)quinones were obtained.[9] Palladium(0)-catalyzed cyclization of the free quinone **22** again gave only low yields of the desired indoloquinone **23**, along with substantial quantities of reduced starting material. Reduction and acetylation followed by cyclization gave fair yields of the acetylated indolohydroquinone **24**, having the requisite 3-carbon fragment for formation of the C ring of the mitosenes in place. Studies to effect cyclization of **24** and related compounds to pyrroloindoloquinones are in progress.

Experimental Section

General. All melting points were taken with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4240 spectrometer. ^{1}H NMR spectra were recorded with a Varian T-60 (60 MHz), an IBM WP270SY (270 MHz), or a Nicolet NTCFT 1180 (360 MHz) spectrometer with tetramethylsilane (Me_4Si) as an internal standard. Routine mass spectra were taken on Vacuum Generators MM16 spectrometer with a Systems Industries interface and disk drive with a digital PDP8A computer at 70 eV. Liquid chromatography was carried out either under moderate pressures (20–60 psi) by using columns of appropriate size packed with Merck silica gel 60 (40–60 mesh) or by using a chromatotron (Harrison Research) radial layer chromatographic device with plates of Kieselgel 60 PF 254 silica gel.

Unless otherwise stated all reactions were run under an argon atmosphere. This was accomplished on a manifold by alternatively evacuating the reaction vessel and pressurizing with argon (five cycles).

For the removal of solvents, "in vacuo" refers to the vacuum achieved by either a water aspirator attached to a Buchi Rotovapor rotary evaporator or by a Welch Duo-Seal vacuum pump attached to a manifold. All solutions of nonvolatile samples were concentrated on a Rotovapor and dried to constant weight on the vacuum pump.

Preparation of 2,5-Bis(*N*-allylamino)-3,6-dibromo-1,4-benzoquinone (1). In a 1 L round-bottomed flask bromanil (18.6 g, 43.2 mmol) was treated with allylamine (15.2 mL, 203 mmol) in 400 mL of ethanol. The mixture was heated to reflux for 4 h, then cooled and stirred for an additional 18 h, then cooled to 0 °C, and filtered. The red crystals were washed with water, ethanol, and ether. Air-drying gave 15.4 g (93%) of the quinone **1** as red crystals, mp 140 °C dec. This material was used without further purification: IR (KBr) 3260 (s, NH), 1600 (m, br, C=O), 1490 (s), 1430 (m), 1330 (m) cm^{-1}.

Preparation of 1,4-Diacetoxy-2,5-dibromo-3,6-bis(*N*-allylacetamido)benzene (2). The quinone **1** (1.00 g, 2.63 mmol) and sodium dithionite (1.20 g, 6.90 mmol) were weighed and placed in an Erlenmeyer flask. The solids were wet with methanol, and then 50 mL of water was added and the slurry warmed to 50 °C under a stream of nitrogen. The mixture was filtered and the precipitate washed with methanol (50 mL) under a stream of nitrogen. This process left red crystals (starting quinone) on the filter paper and white crystals in the filtrate. The filtrate was refiltered under nitrogen to give 0.745 g (75%) of white crystals: IR (Nujol) 3300 (m, NH, OH), 3300–2200 (m, v br, OH, NH), 1490 (m), 1460 (s), 1420 (m), 1380 (m), 1300 (m), 1250 (w), 1200 (w), 1130 (s), 1050 (w), 1020 (w), 990 (w), 920 (m) cm^{-1}. This material lacked sufficient solubility to obtain an NMR spectrum. It readily oxidized and was used immediately after preparation, without further purification.

This hydroquinone (0.745 g, 1.97 mmol) and sodium acetate (50 mg) were added to 10 mL of degassed acetic anhydride under an argon atmosphere. The reaction mixture was heated to reflux under the argon atmosphere, and after 2 h the homogeneous mixture was cooled and poured into 40 mL of water. The reaction mixture was extracted with 40 mL of ether and the ether portion washed with 40 mL of water and 40 mL of 2 N NaOH. The ether solution was dried ($MgSO_4$) and concentrated to give 0.995 g (89%) of white crystals: mp 185 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 6, $NCOCH_3$), 2.31 (s, 6, $OCOCH_3$), 4.10–4.35 (m, 4, NCH_2C), 4.89–5.35 (m, 4, $NCH_2CH{=}CH_2$), 5.54–6.30 (m, 2, $NCH_2CH{=}CH_2$); IR (Nujol) 1790 (s, OC=O), 1685 (s, NC=O), 1180 (s, COC) cm^{-1}. Anal. Calcd for $C_{20}H_{22}Br_2N_2O_6$: C, 43.98; H, 4.06; N, 5.13. Found: C, 44.16; H, 4.20; N, 5.37.

Preparation of 1-Acetyl-3-methyl-4,7-diacetoxy-5-(*N*-allylacetamido)-6-bromoindole (3). The protected hydroquinone **2** (0.227 g, 0.416 mmol) was subjected to the standard cyclization conditions (see below). Separation of the products via medium-pressure liquid chromatography (1:1 hexane–ethyl acetate) gave 0.123 g (64%) of **3**: mp 159.5–161 °C; ^{1}H NMR

(7) Remers, W. A. "Indoles"; Houlihan, W. J., Ed.; Wiley: New York, 1972; part 1, pp 1–226.

(8) This is consistent with earlier observations that bulky secondary amines aminate benzoquinones only once: ref 4a, p 904.

(9) Reference 4a, pp 1104–1109.

($CDCl_3$) δ 1.89 (s, 3, $COCH_3$), 2.28 (d, J = 2 Hz, 3, $ArCH_3$), 2.38 (s, 3, $COCH_3$), 2.45 (s, 3, $COCH_3$), 2.59 (s, 3, $COCH_3$), 4.29 (d, J = 7 Hz, 2, $NCH_2C{=}C$), 4.90–5.40 (m, 2, $NCH_2CH{=}CH_2$), 5.70–6.40 (m, 1, $CH_2CH{=}CH_2$), 7.24 (q, J = 2 Hz, 1, indole H_2); IR (Nujol) 1785, 1755 (C=O), 1680 (NC=O) cm^{-1}. Anal. Calcd for $C_{20}H_{21}BrN_2O_6$: C, 51.63; H, 4.55; N, 6.02. Found: C, 51.82; H, 4.40; N, 6.25.

Preparation of 3,5,6-Tribromotoluquinone (4) and 5-Bromotoluquinone (7). Brominated toluquinones **4** and **7** were prepared by the literature methods.[10] The HBr method was employed for the synthesis of **7**. Both substrates were recrystallized from ethanol prior to use.

Compound **4**: obtained as a bright yellow solid, mp 228 °C (lit.[10] mp 234 °C dec); ^1H NMR (60 MHz, $CDCl_3$) δ 2.32 (s, CH_3); IR ($CDCl_3$) 1681 (C=O), 1662 (C=O), 1571, 1478, 1365, 1280, 1231, 1134, 1030, 982 cm^{-1}.

Compound **7**: obtained as bright yellow needles, mp 97–101 °C (lit.[10] mp 99–100 °C); ^1H NMR (60 MHz, $CDCl_3$) δ 2.11 (d, J = 1.8 Hz, 3, CH_3), 6.77 (q, J = 1.8 Hz, 1, C_3H), 7.23 (s, 1, C_6H); IR ($CDCl_3$) 3150, 3060, 2985, 2975, 2920, 2890, 1670 (C=O), 1630, 1591, 1441, 1430, 1380, 1356, 1344, 1310, 1226, 1199, 1015, 1001 cm^{-1}.

General Procedure for the Amination of 1,4-Benzoquinones. A 25-mL round-bottomed flask equipped with a magnetic stirring bar and a pressure equalizing dropping funnel was charged with the quinone substrate (1 mmol) and absolute ethanol (5 mL). The flask was wrapped in aluminum foil and placed in an ice bath for 5 min. A solution of the desired amine (1–4 mmol) in ethanol (10 mL) was slowly added dropwise to the stirred quinone slurry over the course of 5 min. During the addition a color change from yellow to red or purple was often observed. When the addition of the amine solution was complete, the cooling bath was removed, and the mixture was allowed to warm gradually to room temperature. The disappearance of starting material was monitored by thin-layer chromatography (TLC) on silica gel plates (hexane–ethyl acetate mixtures). Product isolation was accomplished by one of two methods.

Method A: The crude reaction mixture was placed in an ice bath for 0.5 h, and the sides of the flask were scratched with a glass rod to induce precipitation. Suction filtration of the cooled mixture afforded the crude product as a highly colored precipitate, which was dried in vacuo.

Method B: Solvent was removed from the mixture in vacuo to give the product as a crude residue. For large-scale preparations relative proportions of all reagents were maintained, but the quantity of solvent was reduced slightly.

2-Bromo-3-(*N*-allylamino)-5-methyl-1,4-benzoquinone (8). This substrate was prepared as in the general section except that the entire reaction was run under an argon atmosphere, and the relative solvent proportions were altered. Ethanol (125 mL) and 5-bromotoluquinone (20.1 g, 100.0 mmol) were stirred together in a round-bottomed flask under an argon atmosphere and cooled in an ice bath. A degassed solution of allylamine (3.75 mL, 50.1 mmol) in ethanol (500 mL) was slowly added dropwise to the quinone mixture over the course of 2 h, at which time the ice bath was removed and the mixture was allowed to warm gradually to room temperature. After a total of 14 h the product was isolated by concentrating the crude reaction mixture in vacuo to a volume of approximately 50 mL, diluting the mixture with water (150 mL), and cooling the flask to 0 °C in an ice bath. Suction filtration of the cooled mixture afforded a crude purple solid (24.4 g) containing **8**. This material was divided in half, ground together with an equal weight of silica gel (Merck), and dry packed into a small column. Each portion was purified by MPLC (SiO_2; 3:1, hexanes–ethyl acetate) on a large column (49 × 5.5 cm) the first red band collected to give pure **8** (9.9 g, 77%) as a red solid suitably pure for further use. Recrystallization from hexanes gave **8** as pure red needles: mp 76–76.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.02 (d, J = 1.5 Hz, 3, CH_3), 4.35 (m, 2, NCH_2CHCH_2), 4.97–5.37 (m, 2, NCH_2CHCH_2), 5.57–6.23 (m, 1, $NHCH_2CHCH_2$), 6.57 (q, J = 1.5 Hz, 1, C_6H); IR (KBr) 3280 (NH), 3175, 3070, 3000, 2980, 2910, 1675 (C=O), 1650 (C=O), 1558, 1540, 1500, 1470, 1435, 1333, 1315, 1262, 1231, 1204, 1093, 910, 888 cm^{-1}; mass spectrum, m/e (relative intensity) 257:255 (1:1, parent), 255:253 (1:1, $P^+ - 2$ H), 204:202 (1:1, $P^+ - C_3H_3N$), 202:200 (1:1, $P^+ - C_3H_5N$), 176 (57, P^+ – Br), 175 (67, P^+ – HBr), 148 (27, P^+ – Br – CO), 121 (54, P^+ – Br – C_3H_5N).

2-Bromo-3,6-bis(*N*-allylamino)-6-methyl-1,4-benzoquinone (5). This compound was prepared as in the general procedure from 5-bromotoluquinone (5.02 g, 25.0 mmol) and allylamine (5.61 mL, 75.0 mmol) in ethanol (60 mL). After a total reaction time of 5 h, product isolation by method A gave **5** (3.41 g, 44%) as a purple solid. Recrystallization from hexanes afforded the analytically pure material as purple needles: mp 133–134 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.05 (s, 3, CH_3), 4.18 (m, 2, NCH_2CHCH_2), 4.50 (m, 2, NCH_2CHCH_2), 5.25 (m, 4, NCH_2CHCH_2), 5.94 (m, 2, NCH_2CHCH_2), 6.80 (br s, 1, NH), 7.16 (br s, 1, NH); IR (KBr) 3240 (NH), 3080, 1640 (C=O), 1575 (C=N), 1470, 1418, 1400, 1330, 1290, 1266, 1110, 975, 900, 768 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 49.92; H, 4.89; N, 8.74.

2-Bromo-3-(*N*-allylamino)-6-(*N*-benzylamino)-5-methyl-1,4-benzoquinone (9). A solution of benzylamine (0.97 mL, 8.90 mmol) in ethanol (100 mL) was added to aminoquinone **8** (2.27 g, 3.90 mmol) in ethanol (50 mL) at room temperature in the presence of air. After 12 h product isolation by method B afforded the crude product, which was recrystallized from $CHCl_3$ to give **9** (2.01 g, 63%) as a green solid, which was used without further purification, mp 122 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 2.03 (s, 3, CH_3), 3.75 (m, 1, $NCH_aH_bCHCH_2$), 4.45 (m, 1, $NCH_aH_bCHCH_2$), 4.72 (d, J = 6 Hz, 2, NCH_2Ph), 4.97–5.40 (m, 2, NCH_2CHCH_2), 5.50–6.27 (m, 1, NCH_2CHCH_2), 6.27–7.17 (br s, 2, $NHCH_2Ph$, $NHCH_2CHCH_2$), 7.23 (br s, 5, Ar); IR (KBr) 3275 (NH), 3240 (NH), 3031, 3020, 2920, 1571 (C=N), 1548, 1475, 1465, 1456, 1398, 1424, 1417, 1336, 1277, 1091, 985, 931 cm^{-1}.

General Procedure for the Reduction of 1,4-Benzoquinones to Hydroquinones. The reduction of quinones to the corresponding hydroquinones was accomplished by one of two methods. Method A was used for quinones that were easily reduced at room temperature to give hydroquinones that did not easily reoxidize in the presence of air. Quinones that were either not readily reduced by method A or that led to air-sensitive hydroquinone products were reduced by method B.

Method A: The benzoquinone substrate was dissolved in a minimum quantity of methanol or ethanol and transferred to a separatory funnel. A concentrated aqueous solution of sodium dithionite (2.1 equiv) was then transferred to the separatory funnel and the mixture shaken with occasional venting until the quinone color had dissipated. The aqueous phase was extracted with chloroform (3×) or until the extracts were colorless. The combined organic phase was washed with brine and dried ($MgSO_4$). Filtration followed by evaporation of solvent in vacuo gave the hydroquinone, which was used without further purification.

Method B: The benzoquinone substrate was wetted with a small quantity of ethanol (1 mL). A solution of $Na_2S_2O_4$ (2.1 equiv) in a minimum quantity of water (10 mL/mmol of quinone) was added to the quinone slurry. The mixture was then placed under an argon atmosphere and warmed to 60 °C with stirring until the quinone color dissipated. Occasionally, additional portions of $Na_2S_2O_4$ were required before the reduction went to completion. Product isolation was achieved by cooling the mixture to 0 °C to precipitate the product, which was collected by suction filtration under a stream of argon. The air-sensitive solid was washed with small portions of cold water (2×) and either dried in vacuo or used immediately to minimize reoxidation.

3-(*N*-Allylamino)-2-bromo-5-methyl-1,4-hydroquinone (11). Treatment of **8** (4.57 g, 18.6 mmol) with sodium dithionite (7.27 g, 41.8 mmol) in water (26 mL) as described in method B resulted in incomplete reduction after 1 h at 60 °C. Additional sodium dithionite (3.50 g, 20.1 mmol) in water (10 mL) was then added, and the mixture was stirred at room temperature for 12 h. Product isolation gave **11** (3.81 g, 80%) as an air-sensitive pink solid suitable for further use: ^1H NMR (60 MHz, $CDCl_3$) δ 2.18 (s, 3, CH_3), 3.50 (d, J = 6 Hz, 2, NCH_2CHCH_2), 4.47 (br s, 3, NH, OH), 4.93–5.40 (m, NCH_2CHCH_2), 5.60–6.30 (m, 1, NCH_2CHCH_2), 6.57 (s, 1, Ar).

General Procedure for the Acetylation of Hydroquinones. A 50-mL Airlessware flask fitted with a magnetic stirring bar and a serum cap was charged with the hydroquinone (1.0 mmol) and a catalytic quantity of anhydrous NaOAc (approximately 5 mg).

(10) Andres, K. J. M.; Marriam, D. H.; Maxwell, D. R. *J. Chem. Soc.* **1956**, 1844.

The mixture was placed under an argon atmosphere, and excess acetic anhydride (5 mL) was added via syringe. The mixture was heated to 70–110 °C for 1–4 h. When the reaction was judged to be complete by TLC (SiO_2, hexanes–ethyl acetate mixtures) the excess acetic anhydride was removed by evaporative distillation. The residue was dissolved in ether and washed with water, saturated aqueous $NaHCO_3$ (2×), and brine. The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated in vacuo to give the crude product. Further purification was accomplished by recrystallization or liquid chromatography.

6-(*N*-Acetyl-*N*-allylamino)-1-bromo-2,5-diacetoxy-4-methylbenzene (12). Aminoquinone **8** (1.56 g, 6.11 mmol) in ethanol (1 mL) was reduced with sodium dithionite (2.24 g, 12.87 mmol) in water (10 mL) at 60 °C for 1 h by using method B. The resulting pink solid **11** was acetylated in the usual way with acetic anhydride (10 mL) at 80 °C for 10 h. The resulting crude product was purified by chromatotron (4-mm SiO_2; 3:1 to 1:1, hexanes–ethyl acetate, gradient) to give **12** (1.20 g, 51%) as a pink solid.

An alternative preparation of **12** was accomplished directly from 5-bromotoluquinone (2.01 g, 10.0 mmol) without purifying the intermediate species. Amination of **7** (2.01 g, 10.0 mmol) as described for the preparation of **8** gave a crude red solid, which was reduced (method B for reduction) and acetylated (90 °C, 0.66 h; room temperature, 12 h) as usual. Chromatographic purification as before gave **12** (0.63 g, 33%) as a pink solid. Recrystallization from hexanes gave the analytical sample as off-white needles: mp 86.5–87.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.83 (s, 3, $NC(O)CH_3$), 2.17 (s, 3, $ArCH_3$), 2.29 (s, 3, $OC(O)CH_3$), 2.36 (s, 3, $OC(O)CH_3$), 4.12 (dd, J = 7.1 Hz, J = 14.5 Hz, 1, $NCH_aH_bCHCH_2$), 4.24 (m, 1, $NCH_aH_bCHCH_2$), 5.07 (dd, J = 1.2 Hz, J = 10.1 Hz, 1, $NCH_2CHCH_aH_b$), 5.09 (dd, J = 1.2 Hz, J = 17.0 Hz, 1, $NCH_2CHCH_aH_b$), 5.92 (ddt, J = 7.1 Hz, J = 10.1 Hz, J = 17.0 Hz, 1, NCH_2CHCH_2), 7.08 (s, 1, Ar); IR (KBr) 3065, 3000, 2970, 2915, 2840, 1768 (OC=O), 1671 (NC=O), 1460, 1420, 1368, 1305, 1250, 1185, 1138, 1116, 1022, 1000, 910, 890 cm^{-1}; mass spectrum, m/e (relative intensity) 383:381 (1:1, parent), 343:341 (1:1, $P^+ - C_2H_2O$), 326:324 (1:1, P^+ – OAc), 304 (85, P^+ – Br), 301:299 (1:1, $P^+ - C_2H_2O$), 262 (23, P^+ – Br – C_2H_2O), 259:257 (1:1, $P^+ - 3C_2H_2O$), 220 (57, P^+ – Br – $2C_2H_2O$), 218:216 (1:1, P^+ – allyl – $3C_2H_2O$). Anal. Calcd for $C_{16}H_{18}NO_5Br$: C, 50.02; H, 4.72; N, 3.65. Found: C, 50.24; H, 4.96; N, 3.82.

General Procedure for Intramolecular Pd(0)-Catalyzed Cyclization Reactions. A thick-walled sealed tube or Fischer–Porter tube was fitted with a magnetic stirring bar and charged with $Pd(OAc)_2$ (1–10 mol %), tri-*o*-tolylphosphine (2–6 equiv based on Pd), and dry degassed acetonitrile (1 mL). The mixture was flushed with argon and stirred for 5 min. The substrate (1.0 mmol) was then added either as a solid or as an acetonitrile (5–9 mL) solution. If the substrate was added as a solid the walls of the tube were subsequently washed with acetonitrile (5–9 mL). Triethylamine (1.1–2.5 mmol) was introduced via syringe. The tube was then flushed with argon, sealed, and heated to the desired temperature (50–110 °C) with stirring. This portion of the reaction was performed behind a blast shield as a safety precaution. Initially upon heating a color change to coffee brown was generally observed. The appearance of Pd(0) as either a mirror or a finely divided black precipitate often signaled catalyst deactivation or completion of the reaction. The tube was then cooled, and the mixture was analyzed by TLC (SiO_2; hexanes–ethyl acetate mixtures). For completed reactions product isolation was effected by filtering the crude mixture through a pad of Celite to remove Pd(0) and concentration of the filtrate in vacuo. Alternatively, the crude mixture was diluted with ether prior to filtration to precipitate and remove Et_3NHX salts as well. Further purification was accomplished by liquid chromatography on silica gel.

For reactions that were incomplete due to premature catalyst deactivation a number of variations were found to be useful. Lower temperatures and higher relative phosphine concentrations were found to stabilize the catalyst to some extent and to drive some reactions to completion. Alternatively, more catalyst was added after initial deactivation according to an earlier procedure.[2] Repetitive catalyst additions (up to three) over the course of several days were found to give higher yields of cyclized products with more efficient use of the catalyst in many instances. The introduction of additional catalyst was accomplished by first cooling the reaction flask to room temperature. Preweighed $Pd(OAc)_2$ and tri-*o*-tolylphosphine were then added as solids or as a combined solution in acetonitrile (3–5 mL) in the relative proportions as before. If the catalyst was added as a solid the walls of the reaction vessel were washed with acetonitrile (3–5 mL) to help quantify the transfer. The vessel was flushed with argon, resealed, and reheated as before.

3,6-Dimethylindole-4,7-dione (10). A. From 8. Quinone **8** (0.518 g, 2.00 mmol), $Pd(OAc)_2$ (0.090 g, 0.40 mmol), tri-*o*-tolylphosphine (0.304 g, 1.00 mmol), Et_3N (0.42 mL, 3.0 mmol), and 12 mL of CH_3CN were mixed together in a sealed tube, flushed with argon, and heated to 75 °C for 15 h. The mixture was cooled and filtered through Celite. Solvent was removed from the filtrate in vacuo and the residue was purified by liquid chromatography (SiO_2; 5:1 hexanes–ethyl acetate) to give **10** (0.108 g, 31%) as a pale yellow solid.

B. From 11. Hydroquinone **11** (0.200 g, 0.78 mmol), $Pd(OAc)_2$ (12 mg, 0.053 mmol), tri-*o*-tolylphosphine (45 mg, 0.15 mmol), Et_3N (0.29 mL, 2.09 mmol), and 7 mL of CH_3CN were heated together at 105 °C for 1.17 h in a sealed tube. Product isolation as described in the previous preparation (from **8**) followed by purification by chromatotron (1-mm SiO_2; 3:1 hexanes–ethyl acetate) gave **10** (49 mg, 36%) as a yellow solid.

C. From 21. Acylated hydroquinone **21** (0.208 g, 0.67 mmole, $Pd(OAc)_2$ (8.7 mg, 0.039 mmol), tri-*o*-tolylphosphine (31 mg, 0.10 mmol), Et_3N (0.20 mL, 1.4 mmol), and 6 mL of CH_3CN were reacted together in the usual way at 105 °C for 5.2 h. Product isolation as before gave the crude product, which was purified by chromatotron (2-mm SiO_2; 3:1 hexanes–ethyl acetate) to give **10** as a yellow solid (40.1 mg, 34%).

Recrystallization from hexanes–ethyl acetate gave an analytical sample of **10** as a bright yellow powder: mp 164 °C dec; ^1H NMR (360 MHz, $CDCl_3$) δ 2.07 (s, 3, C_3CH_3), 2.33 (s, 3, C_6CH_3), 6.40 (s, 1, C_5H), 6.80 (s, 1, C_2H), 9.20 (br s, 1, NH); IR (KBr) 3180 (NH), 3030, 2940, 2920, 2850, 1632 (C=O), 1610, 1560, 1510, 1476, 1412, 1390, 1372, 1323, 1301, 1276, 1252, 1221, 1192, 1130, 1078, 1030, 997, 930, 890, 830, 795, 776, 753, 691, 668, 600 cm^{-1}; mass spectrum, m/e (relative intensity) 175 (100, parent), 174 (14, P^+ – H), 147 (12, P^+ – CO), 146 (17, P^+ – CHO), 118 (21, P^+ – CO – CHO), 107 (29, P^+ – CO – C_3H_4). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.37; H, 5.41; N, 7.79.

1-Acetyl-4,7-diacetoxy-3,6-dimethylindole (13). A mixture of **12** (1.20 g, 3.14 mmol), $Pd(OAc)_2$ (18 mg, 0.080 mmol), tri-*o*-tolylphosphine (71 mg, 0.23 mmol), Et_3N (0.91 mL, 6.55 mmol), and 6 mL of CH_3CN was flushed with argon and heated in a sealed tube at 75–80 °C for 12 h. The mixture was then cooled, and more $Pd(OAc)_2$ (18 mg, 0.080 mmol), tri-*o*-tolylphosphine (71 mg, 0.23 mmol), and 3 mL of CH_3CN were added to the vessel. The mixture was flushed with argon and reheated to 80 °C for 9 h. The crude mixture was filtered through Celite, and the Celite was washed with ethyl acetate. The solvent was removed from the filtrate in vacuo to yield a crude brown solid. Separation by chromatotron (4-mm SiO_2; 3:1 hexanes–ethyl acetate → ethyl acetate, gradient) gave **13** (0.84 g, 89%) having R_f 0.4 (SiO_2; 1:1 hexanes–ethyl acetate). Recrystallization from hexanes afforded the analytical sample as an off-white powder; mp 205.6–206 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.27 (s, 3, $ArCH_3$), 2.29 (s, 3, $ArCH_3$), 2.35 (s, 3, $OC(O)CH_3$), 2.37 (s, 3, $OC(O)CH_3$), 2.55 (s, 3, $NC(O)CH_3$), 6.89 (s, 1, C_2H), 7.03 (s, 1, C_5H); IR (KBr) 3135, 2950, 2920, 2855, 1769 (OC=O), 1762 (OC=O), 1732 (NC=O), 1491, 1440, 1385, 1368, 1341, 1258, 1202, 1189, 1159, 1078, 1056, 1002, 965, 936, 895, 790, 751 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.20; H, 5.88; N, 4.59.

5-(*N*-Allylamino)-3,6-dimethylindole-4,7-dione (14) and 6-(*N*-Allylamino)-7-methylquinoline-5,8-dione (15). A mixture of **5** (50 mg, 0.16 mmol), $Pd(OAc)_2$ (2 mg, 0.0098 mmol), tri-*o*-tolylphosphine (8 mg, 0.025 mmol), Et_3N (0.027 mL, 0.20 mmol), and 3 mL of CH_3CN was flushed with argon and heated in a sealed tube at 95 °C for 18 h. After filtration through Celite, the filtrate was concentrated in vacuo. The residue was purified by liquid chromatography (SiO_2; 3:1 hexanes–ethyl acetate for **14**, R_f 0.40; ethyl acetate for **15**, low R_f) to give **14** (15 mg, 43%) as a purple solid and **15** (9 mg, 26%) as an orange solid.

Recrystallization from ether–hexanes afforded an analytical sample of **14** as a red solid; mp 201–202 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.07 (s, 3, C_6CH_3), 2.20 (s, 3, C_3CH_3), 4.13 (m, 2, NCH_2CHCH_2), 5.26 (m, 2, NCH_2CHCH_2), 5.92 (m, 1,

NCH_2CHCH_2), 6.60 (s, 1, C_2H); IR (KBr) 3300 (NH), 3160 (NH), 3140 (NH), 3050, 3015, 2845, 1656 (C=O), 1590, 1554, 1520, 1503, 1478, 1460, 1431, 1300, 1351, 1304, 1290, 1279, 1230, 1078, 972, 712, 775, 730 cm^{-1}; mass spectrum, m/e (relative intensity) 230 (100, parent), 215 (90, P^+ - Me), 201 (21, P^+ - CHO), 189 (16, P^+ - allyl). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.80; H, 6.18; N, 12.30.

Compound **15**: no elemental analysis was obtained for **15** due to its instability and its spectroscopic similarity to fully characterized analogues prepared by another route;[11] mp 109–112.5 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 2.29 (s, 3, CH_3), 4.20 (m, 2, NCH_2CHCH_2), 5.28 (m, 2, NCH_2CHCH_2), 5.82 (br s, 1, NH), 5.96 (m, 1, NCH_2CHCH_2), 7.54 (dd, J = 1.7 Hz, J = 7.8 Hz, 1, C_3H), 8.32 (dd, J = 4.8 Hz, J = 7.8 Hz, 1, C_4H), 8.97 (dd, J = 1.7 Hz, J = 4.8 Hz, 1, C_2H); IR (KBr) 3350 (NH), 3065, 2915, 1671 (C=O), 1623, 1595, 1560, 1520, 1505, 1455, 1421, 1395, 1368, 1325, 1270, 1218, 1111, 1085, 983, 905, 745, 676 cm^{-1}; mass spectrum, m/e (relative intensity) 228 (27, parent) 227 (19, P^+ - H), 226 (66, P^+ - 2H), 213 (61, P^+ - NH(allyl)); UV–vis ($CHCl_3$) 465, 270, 242 (λ_{max}) nm.

2,5-Bis(*N*-acetyl-*N*-allylamino)-1-bromo-3,6-diacetoxy-4-methylbenzene (16). Diaminoquinone **5** (0.430 g, 1.38 mmol) was reduced with sodium dithionite (0.505 g, 2.90 mmol) in water (15 mL) at 55 °C for 6 h by using method B to give the crude hydroquinone as a pink solid. The hydroquinone was immediately treated with acetic anhydride (10 mL) and a small quantity of anhydrous sodium acetate at 105 °C for 15 h in the usual way. The crude mixture was then allowed to cool gradually to room temperature over the course of 12 h. Product isolation gave **16** (0.492 g, 74%) as a pink solid suitably pure for further use. Recrystallization from hexanes afforded the analytical sample as colorless crystals: mp 138–138.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.77 (s, 3, $NC(O)CH_3$), 1.83 (s, 3, $NC(O)CH_3$), 2.02 (s, 3, $ArCH_3$), 2.28 (s, 3, $OC(O)CH_3$), 2.31 (s, 3, $OC(O)CH_3$), 3.80–4.60 (m, 4, NCH_2CHCH_2), 5.04–5.12 (m, 4, NCH_2CHCH_2), 5.84–5.95 (m, 2, $NCH_2CH{=}CH_2$); IR ($CDCl_3$) 3150, 3080, 3010, 2975, 2915, 1775 (OC=O), 1665 (NC=O), 1650 (NC=O), 1460, 1430, 1412, 1365, 1330, 1278, 1236, 1170, 1146, 1109, 1051, 1030, 1005 cm^{-1}; mass spectrum, m/e (relative intensity) 482:480 (1:1, parent), 440:438 (1:1, P^+ - C_2H_2O), 423:421 (1:1, P^+ - OAc), 398:396 (1:1, P^+ - $2C_2H_2O$), 380:378 (1:1, P^+ - Ac - OAc), 356:354 (P^+ - $3C_2H_2O$), 273:271 (1:1, P^+ - $3C_2H_2O$ - 2 allyl), 191 (30, P^+ - C_2H_2O - 2 allyl - HBr). Anal. Calcd for $C_{21}H_{25}O_6N_2Br$: C, 52.40; H, 5.24; N, 5.82. Found: C, 52.47; H, 5.20; N, 5.63.

1-Acetyl-5-(*N*-acetyl-*N*-allylamino)-4,7-diacetoxy-3,6-dimethylindole (17) and 1-Acetyl-5-(*N*-acetyl-*N*-allylamino)-4,7-diacetoxy-6-methyl-3-methylene-2,3-dihydroindole (18). A mixture of **16** (0.481 g, 1.00 mmol), $Pd(OAc)_2$ (12 mg, 0.051 mmol), tri-*o*-tolylphosphine (48 mg, 0.16 mmol), Et_3N (0.29 mL, 2.09 mmol), and 6 mL of CH_3CN was flushed with argon and then heated in a sealed tube at 105 °C for 2 h. The mixture was cooled and filtered through Celite, and the Celite was washed with ether. The filtrate was gravity filtered to remove precipitated Et_3NHBr (0.112 g, 61%), and the filtrate was concentrated in vacuo to give a pink solid (0.519 g). Purification was performed by chromatotron (2-mm SiO_2; 2:1 ethyl acetate–hexanes). The UV-active bands at R_f 0.32 and 0.14 contained **17** (0.304 g, 76%) and **18** (0.083 g, 21%), respectively, both as cream colored solids. Analytical samples were obtained by recrystallization of the crude solids from hexanes–ethyl acetate.

Indole **17**: obtained as a colorless powder, mp 165.5–166.5 °; ^1H NMR (360 MHz, $CDCl_3$) δ 1.79 (s, 3, $N(CH_2CHCH_2)C(O)CH_3$), 2.15 (s, 3, $ArCH_3$), 2.25 (s, 3, $ArCH_3$), 2.33 (s, 3, $OC(O)CH_3$), 2.39 (s, 3, $OC(O)CH_3$), 2.57 (s, 3, $NC(O)CH_3$), 3.80–4.00 (m, 1, $NCH_aH_bCHCH_2$), 4.40–4.60 (m, 1, $NCH_aH_bCHCH_2$), 5.13 (m, 2, NCH_2CHCH_2), 5.91 (m, 1, NCH_2CHCH_2), 7.12 (s, 1, Ar); IR (KBr) 3145, 3075, 3015, 2975, 2930, 1764 (OC=O), 1736 (indole NC=O), 1669 (NC=O), 1475, 1435, 1415, 1390, 1372, 1348, 1335, 1279, 1258, 1210, 1190, 1161, 1082, 1045, 1005, 1000, 960, 940, 882, 790, 751, 716, 638 cm^{-1}; mass spectrum, m/e (relative intensity) 400 (8, parent), 358 (45, P^+ - C_2H_2O), 341 (13, P^+ - OAc), 316 (66, P^+ - 2 C_2H_2O), 273 (50, P^+ - C_2H_2O-Ac), 233 (100, P^+ - $3C_2H_2O$ - allyl), 191 (35, P^+ - $4C_2H_2O$ - allyl). Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 63.07; H, 6.07; N, 6.77.

Compound **18**: mp 130–134.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.80 (s, 3, $N(CH_2CHCH_2)C(O)CH_3$), 2.09 (s, 3, $NC(O)CH_3$), 2.23 (s, 3, $ArCH_3$), 2.31 (s, 3, $OC(O)CH_3$), 2.31 (s, 3, $OC(O)CH_3$), 3.82 (m, 1, $NCH_aH_bCHCH_2$), 4.48 (m, 1, $NCH_aH_bCHCH_2$), 4.71 (s, 2, $NCH_2C(Ar)C{=}$), 5.07–5.12 (m, 2, NCH_2CHCH_2), 5.22 (m, 1, $NCH_2C(Ar)CH_aH_b$), 5.42 (d, J = 2.3 Hz, 1, $NCH_2C(Ar)CH_aH_b$), 5.88 (m, 1, NCH_2CHCH_2); IR (KBr) 2970, 2925, 1773 (OC=O), 1694 (NC=O), 1660 (NC=O), 1468, 1420, 1395, 1372, 1304, 1279, 1260, 1200, 1180, 1172, 1081, 1070, 1045, 1035, 1013, 980, 940, 926, 879, 860 cm^{-1}; mass spectrum, m/e (relative intensity) 400 (24, parent), 358 (41, P^+ - C_2H_2O), 341 (50, P^+ - OAc), 316 (77, P^+ - $2C_2H_2O$), 299 (22, P^+ - C_2H_2O - OAc), 274 (60, P^+ - $3C_2H_2O$), 233 (100, P^+ - $3C_2H_2O$ - allyl), 191 (45, P^+ - $4C_2H_2O$ - allyl). Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.80; H, 6.23; N, 6.85.

5-(*N*-Benzylamino)-3,6-dimethylindole-4,7-dione (19) and 6-(*N*-Benzylamino)-7-methylquinoline-5,8-dione (20). A mixture of quinone **9** (0.107 g, 0.30 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), tri-*o*-tolylphosphine (19 mg, 0.06 mmol), Et_3N (0.05 mL, 0.37 mmol), and 3 mL of CH_3CN was flushed with argon and heated at 65 °C for 15 h in a sealed tube. The crude mixture was cooled and filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by liquid chromatography (SiO_2; 3:1 hexanes–ethyl acetate for **19**; ethyl acetate for **20**) to give indole **19** (41 mg, 49%) as a purple solid and the quinoline **20** (19 mg, 23%) as an orange solid.

Indoloquinone **19**: recrystallization from hexanes–ethyl acetate gave an analytical sample of **19** as a purple powder, mp 180 °C dec; ^1H NMR (360 MHz, $CDCl_3$) δ 2.09 (s, 3, C_6CH_3), 2.29 (s, 3, C_3CH_3), 4.72 (d, J = 6.1 Hz, 2, $PhCH_2NH$), 6.24 (br s, 1, $PhCH_2NH$), 6.63 (br s, 1, C_2H), 7.27–7.39 (m, 5, Ar), 10.07 (br s, 1, indole NH); IR (KBr) 3295 (NH), 3145 (NH), 3050, 3010, 2930, 2830, 1662 (C=O), 1590, 1550, 1498, 1472, 1450, 1425, 1380, 1356, 1303, 1279, 1228, 1078, 981, 773, 714 cm^{-1}; mass spectrum, m/e (relative intensity) 282 (9, P^+ + 2H), 280 (15, parent), 189 (14, P^+ - C_7H_7), 175 (12, P^+ - C_7H_7N), 91 (47, $C_7H_7^+$). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.63; H, 5.98; N, 10.24.

Compound **20**: this product was unstable and underwent gradual decomposition with loss of the *N*-benzyl group to form 6-amino-7-methylquinoline-5,8-dione identical in all respects with material prepared by another route.[11] Due to its instability and its spectroscopic similarity (NMR) to fully characterized analogues, compound **20** was only characterized by NMR spectroscopy; ^1H NMR (270 MHz, $CDCl_3$) δ 2.29 (s, 3, CH_3), 4.78 (d, J = 6.3 Hz, 2, $NHCH_2Ph$), 5.98 (br s, 1, NH), 7.28–7.42 (m, 5, Ar), 7.54 (dd, J = 4.6 Hz, J = 7.8 Hz, 1, C_3H), 8.32 (dd, J = 1.4 Hz, J = 7.8 Hz, 1, C_4H), 8.97 (dd, J = 1.4 Hz, J = 4.6 Hz, 1, C_2H).

3-(*N*-Acryloyl-*N*-allylamino)-2-bromo-5-methyl-1,4-hydroquinone (21). A 50-mL Airlessware flask was charged with the aminohydroquinone **11** (0.611 g, 2.37 mmol) and 4A molecular sieve (15 mL dry volume). The flask was fitted with a rubber serum cap and placed under an argon atmosphere. Dry, freshly distilled, and degassed THF (10 mL) was transferred to the flask via cannula, and the apparatus was gently shaken to facilitate dissolution of the substrate. The mixture was placed in an ice bath, and acryloyl chloride (0.21 mL, 2.60 mmol) was then added dropwise via syringe. Upon complete addition the flask was removed from the ice bath and allowed to stand with occasional shaking at room temperature for 12 h. The mixture was then filtered through a large wire mesh to remove the sieves, and the filtrate was concentrated in vacuo to afford the crude product. Purification by chromatotron (2-mm SiO_2; 3:1 → 1:1 hexanes–ethyl acetate, gradient) gave **21** as a colorless oily solid (0.600 g, 81%). Recrystallization from ethyl acetate–hexanes gave an analytical sample as a colorless solid: mp 141.5–164 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.24 (s, 3, CH_3), 3.92 (dd, J = 8.0 Z, J = 14.2 Hz, 1, $NCH_aH_bCHCH_2$), 4.68 (dd, J = 6.4 Hz, J = 14.2 Hz, 1, $NCH_aH_bCHCH_2$), 5.13–5.24 (m, 2, NCH_2CHCH_2), 5.59 (dd, J = 1.6 Hz, J = 10.4 Hz, 1, $NC(O)CHCH_aH_b$), 5.93 (dd, J = 10.4 Hz, J = 16.8 Hz, 1, $NC(O)CHCH_2$), 5.96–6.05 (m, 1, NCH_2CHCH_2), 6.44 (dd, J = 1.6 Hz, J = 16.8 Hz, 1, $NC(O)CHCH_aH_b$), 6.91 (s, 1, Ar); IR (KBr) 3500 (OH), 3325 (OH), 3080, 3020, 2975, 2920, 2840, 1648 (NC=O), 1612, 1590, 1466, 1433, 1409, 1351, 1330, 1278,

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1260, 1231, 1197, 1172, 1140, 1098, 1056, 1010, 998, 986, 965, 925, 910, 861, 846, 818, 790, 745 cm^{-1}. Anal. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.02; H, 4.52; N, 4.49. Found: C, 49.81; H, 4.32; N, 4.44.

2-Bromo-3-(*N*,*N*-diallylamino)-5-methyl-1,4-benzoquinone (22). This compound was synthesized in the usual way from 5-bromotoluquinone (201 mg, 1.00 mmol) and diallylamine (0.15 mL, 1.18 mmol) in ethanol (15 mL). After 4 h the product was isolated by method B to give a crude purple oil, which was purified by liquid chromatography (SiO_2; 3:1 hexanes–ethyl acetate). The first purple band (R_f 0.50) contained a mixture of **22** and the corresponding hydroquinone as a purple oil (103 mg, 35%). The oil was dissolved in ethanol (5 mL), transferred to a 60-mL separatory funnel, and shaken with a solution of $FeCl_3 \cdot 6H_2O$ (95 mg, 0.35 mmol) in 0.1 N HCl (0.5 mL) and water (5 mL). The mixture was then washed with chloroform (3×). The combined organic phase was washed with saturated aqueous Na_2CO_3 (2×), water, and brine and dried ($MgSO_4$). Filtration followed by concentration of the filtrate in vacuo gave **22** as a light-sensitive purple oil (96 mg, 32%) suitably pure for further use.

Compound **22**: ^1H NMR (60 MHz, $CDCl_3$) δ 2.02 (d, J = 3 Hz, 3, CH_3), 3.97 (d, J = 7 Hz, 4, NCH_2CHCH_2), 5.02 (m, 2, NCH_2CHCH_2), 5.25 (m, 2, NCH_2CHCH_2), 5.77 (m, 2, NCH_2CHCH_2), 6.58 (q, J = 3 Hz, 1, C_6H); IR (CCl_4) 3085, 3010, 2985, 2960, 2920, 2870, 2850, 1668 (C=O), 1640 (C=O), 1592, 1556, 1439, 1420, 1380, 1342, 1278, 1225, 1191, 1155, 1130, 1111, 1070, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 297:295 (1:1, parent), 256:254 (1:1, $P^+ - C_3H_5$), 216 (91, $P^+ - Br$).

1-Allyl-3,6-dimethylindole-4,7-dione (23). A mixture of quinone **22** (0.296 g, 1.00 mmol), $Pd(OAc)_2$ (13 mg, 0.060 mmol), tri-*o*-tolylphosphine (34 mg, 0.11 mmol), Et_3N (0.15 mL, 1.1 mmol), and 6 mL of CH_3CN was flushed with nitrogen and heated in a sealed tube at 105 °C for 1.25 h. The crude mixture was cooled, diluted with 20 mL ether, and filtered through Celite. The Celite was washed with additional ether. The resulting filtrate was gravity filtered to remove precipitated $Et_3N \cdot HBr$. The filtrate was concentrated in vacuo to give a residual brown oil. Purification by chromatotron (2-mm SiO_2: 3:1 hexanes–ethyl acetate) gave an amber oil (0.101 g) containing **23** (14% by NMR) and reduced starting material **22** (24% by NMR). Pure **23** could be obtained by treating the crude reaction mixture with $FeCl_3$/0.1NH_4Cl. Liquid chromatography (SiO_2: 2:1 hexanes–ether) gave pure **23** as a yellow solid with significant loss of material. Recrystallization from ether–hexanes gave an analytical sample as yellow needles: mp 86.5–87.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.04 (d, J = 1.5 Hz, 3, C_6CH_3), 2.29 (s, 3, C_3CH_3), 4.92 (d, J = 5.6 Hz, 2, NCH_2CHCH_2), 5.11 (dd, J = 1.0 Hz, J = 17.1 Hz, 1, $NCH_2CHCH_aH_b$), 5.22 (dd, J = 1.0 Hz, J = 9.9 Hz, 1, $NCH_2CHCH_aH_b$), 5.98 (m, 1, NCH_2CHCH_2), 6.37 (q, J = 1.5 Hz, 1, C_5H), 6.65 (s, 1, C_2H); IR (KBr) 3110, 3075, 2940, 2915, 1661 (C=O), 1640 (C=O), 1610, 1496, 1397, 1375, 1240, 1209, 931 cm^{-1}; mass spectrum, m/e (relative intensity) 215 (100, parent), 200 (58, $P^+ - Me$), 186 (16, $P^+ - CHO$), 174 (24, $P^+ - allyl$), 172 (18, $P^+ - CO - Me$), 146 (19, $P^+ - CO - allyl$). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.34; H, 6.16; N, 6.45.

1-Bromo-2,5-diacetoxy-6-(*N*,*N*-diallylamino)-4-methylbenzene (25). Quinone substrate **22** (0.895 g, 3.02 mmol) in ethanol (15 mL) was reduced with sodium dithionite (0.657 g, 3.78 mmol) in water (20 mL) by using method A to give the crude hydroquinone as an air-stable brown oil. Acetylation with acetic anhydride (10 mL) as described earlier (120 °C, 1.5 h; room temperature, 12 h) gave a crude amber oil, which was purified by chromatotron (2-mm SiO_2; 3:1 hexanes–ethyl acetate; R_f 0.43) to give **25** (472 mg, 41%) as an amber oil suitably pure for further use. Evaporative distillation [117 °C (0.005 mm)] gave an analytical sample.

Alternatively, 5-bromotoluquinone (6.08 g, 30.2 mmol) was aminated with diallylamine (4.42 mL, 24.8 mmol) in ethanol as described earlier in the general amination section (method B). Without purification, the crude product was reduced (method A) and acetylated as before to give crude **25**, which was triturated with hot hexanes. Concentration of the filtrate in vacuo gave **25** (3.54 g, 31%). The remaining insoluble residue was subjected to evaporative distillation as before to give additional **25** (1.40 g, 12%). Thus, **25** was isolated in 43% overall yield from this three-step procedure: ^1H NMR (60 MHz, CCl_4) δ 2.03 (s, 3, $ArCH_3$), 2.18 (s, 6, $OC(O)CH_3$), 3.57 (d, J = 6 Hz, 4, NCH_2CHCH_2), 4.82–5.22 (m, 4, NCH_2CHCH_2), 5.38–5.95 (m, 2, NCH_2CHCH_2), 6.68 (s, 1, Ar); IR (CCl_4) 3080, 3010, 2980, 2930, 2890, 2840, 1771 (C=O), 1642, 1573, 1465, 1430, 1418, 1370, 1185, 1085, 1128, 1110 cm^{-1}; mass spectrum, m/e (relative intensity) 383:381 (1:1, parent), 342:340 (1:1, $P^+ - allyl$), 302 (34, $P^+ - Br$), 300:298 ($P^+ - 2$ allyl), 258:256 (1:1, $P^+ - 2$ allyl – Ac). Anal. Calcd for $C_{17}H_{20}O_4NBr$ C, 53.42; H, 5.27; N, 3.66. Found: C, 53.32; H, 5.41; N, 3.59.

1-Allyl-4,7-diacetoxy-3,6-dimethylindole (24). A mixture of substrate **25** (0.851 g, 2.23 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), tri-*o*-tolylphosphine (39 mg, 0.13 mmol), Et_3N (0.65 mL, 4.7 mmol), and 10 mL of CH_3CN was flushed with argon and then heated in a sealed tube at 105 °C for 21 h. After the mixture was cooled to room temperature TLC analysis (SiO_2: 3:1 hexanes–ethyl acetate) indicated the presence of unreacted starting material (R_f 0.36). Additional $Pd(OAc)_2$ (14 mg, 0.061 mmol), tri-*o*-tolylphosphine (43 mg, 0.14 mmol), Et_3N (0.65 mL, 4.7 mmol)e, and 5 mL of CH_3CN were added to the crude mixture. The reaction vessel was then flushed with argon, sealed, and heated to 105 °C for 23 h. The resulting mixture was cooled and filtered through Celite. The Celite was washed with ether, and the filtrate concentrated in vacuo to give a crude brown oil (1.65 g). This material was purified by chromatotron (4-mm SiO_2; 1:1 hexanes–ether); the band having R_f 0.22 was collected and gave **24** (0.522 g, 78%) as a cream-colored solid. Recrystallization from hexanes–ether gave an analytical sample as colorless needles: mp 133.5–134 °C; ^1H NMR (360 MHz, acetone-d_6) δ 2.15 (s, 3, C_6CH_3), 2.26 (d, J = 0.8 Hz, 3, C_3CH_3), 2.31 (s, 3, $OC(O)CH_3$), 2.36 (s, 3, $OC(O)CH_3$), 4.79 (br s, 2, NCH_2CHCH_2), 4.90 (dd, J = 1.5 Hz, J = 17.1 Hz, 1, $NCH_2CHCH_aH_b$), 5.09 (dd, J = 1.5 Hz, J = 10.3 Hz, 1, $NCH_2CHCH_aH_b$), 6.03 (ddt, J = 10.3 Hz, J = 17.1 Hz, J = 5.0 Hz, 1, NCH_2CHCH_2), 6.60 (s, 1, Ar), 6.85 (s, 1, Ar), IR (KBr) 3070, 2980, 2970, 2940, 2890, 1751 (C=O), 1629, 1559, 1508, 1450, 1424, 1366, 1319, 1220, 1204, 1186, 1134, 1061, 1013, 922, 945, 920, 895, 840, 808, 745 cm^{-1}; mass spectrum, m/e (relative intensity) 301 (19, parent), 259 (21, $P^+ - C_2H_2O$), 217 (100, $P^+ - 2C_2H_2O$). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.69; H, 6.46; N, 4.68.

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Registry No. **1**, 98217-02-8; 1-hydroquinone, 98217-03-9; **2**, 98217-04-0; **3**, 98217-05-1; **4**, 29666-53-3; **5**, 98217-07-3; 5-hydroquinone, 98217-15-3; **6**, 98217-02-8; **7**, 13070-25-2; **8**, 98217-06-2; **9**, 98244-65-6; **10**, 98217-10-8; **11**, 98217-08-4; **12**, 98217-09-5; **13**, 98217-12-0; **14**, 98217-13-1; **15**, 98217-14-2; **16**, 98217-16-4; **17**, 98217-17-5; **18**, 98217-18-6; **19**, 98217-19-7; **20**, 98217-20-0; **21**, 98217-11-9; **22**, 98217-21-1; **22**-hydroquinone, 98217-22-2; **23**, 98217-23-3; **24**, 98217-25-5; **25**, 98217-24-4; CH_2=$CHCH_2NH_2$, 107-11-9; $PhCH_2NH_2$, 100-46-9; CH_2=CHCOCl, 814-68-6; (CH_2=$CHCH_2)_2NH$, 124-02-7; $Pd(OAc)_2$, 3375-31-3; CH_3CN, 75-05-8; Pd, 7440-05-3; bromanil, 488-48-2; tri-*o*-tolylphosphine, 6163-58-2.