Substituted Quinone Synthesis by Palladium–Copper Cocatalyzed Cross-Coupling of Stannylquinones with Aryl and Heteroaryl Iodides

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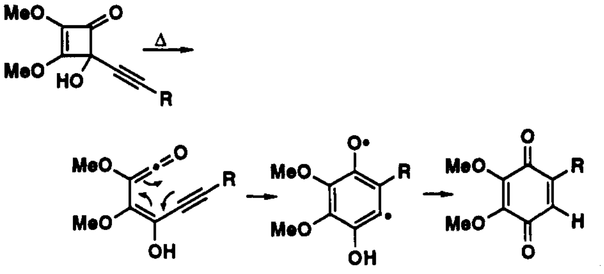
Received August 11, 1992

A general and high-yielding route to a variety of aryl- and heteroaryl-substituted quinones is now available via the palladium–copper cocatalyzed cross-coupling of stannylquinones with aryl and heteroaryl iodides. Using this technology a number of novel aromatic- and heteroaromatic-substituted quinones were produced. Mechanistic insight is presented into the various catalytic systems used.

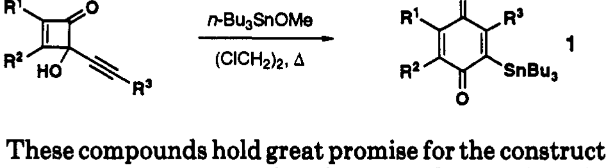
Introduction

Quinones represent an important class of biologically active molecules that are widespread in nature. Medicinal agents, both naturally-occurring and synthetic, have been developed that are based on the quinone structure.[1-5] Accordingly, it is important to uncover simple yet powerful methods for the synthesis of substituted quinones that can form the foundation upon which new medicinal agents can be constructed.

Historically, most methods for the synthesis of quinones have relied on elaboration of a preexisting aromatic or heteroaromatic core. In recent years, however, novel and useful procedures for construction of quinones (and phenols) have appeared that proceed via various unsaturated ketene intermediates.[6-18] In one useful variant of quinone synthesis via unsaturated ketene intermediates, Moore discovered that certain types of 4-alkynyl-4-hydroxycyclobutenones, prepared by addition of acetylide anions to squaric acid esters, transform directly into quinones on thermolysis (eq 1).[19,20] This reaction is thought to occur via closure of an enynylketene to a diradical that reorganizes to the quinone. It was subsequently shown that thermolysis of 4-alkynyl-4-hydroxycyclobutenones in dichloroethane in the presence of $n\text{-Bu}_3\text{SnOMe}$ directly produced stannylquinones 1 (eq 2).[21]



(1)



(2)

These compounds hold great promise for the construction of complex quinones by direct carbon–carbon bond formation onto the quinone nucleus using palladium-catalyzed cross-coupling technology (Scheme I). It has already been shown that stannylquinones undergo palladium-catalyzed allylation[21] and oxidative dimerization.[22] Documented herein is an efficient method for the direct attachment of substituted aromatic and heteroaromatic groups to the quinone core.

Results and Discussion

Exploratory studies of the cross-coupling of 2,3,5-trimethyl-6-(tri-n-butylstannyl)benzo-1,4-quinone with iodobenzene using various palladium catalysts with added ligands provided the following insights into the reaction:

(1) In a variety of solvents, triphenylphosphine-based palladium catalysts did not support an efficient and rapid cross-coupling.

(2) Effective catalysis of cross-coupling was observed using triphenylarsine/$\text{Pd}_2(\text{dba})_3$ (dba = dibenzylideneacetone) in DMF at 60 °C with cocatalytic CuI. The use of triphenylarsine as a supporting ligand for palladium-catalyzed cross-coupling was described by Farina,[23] although the addition of cocatalytic CuI was found to be essential for the current reactions.[22,24-26] This represents

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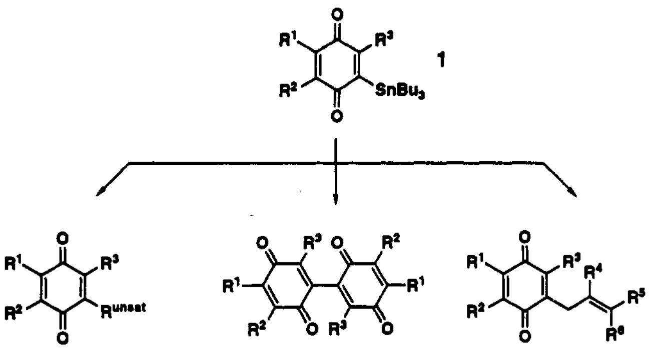
0022-3263/93/1958-0408$04.00/0

Scheme I



R^{unsat} = aryl, heteroaryl, vinyl

yet one more example of the beneficial effect of cocatalytic CuI on palladium-catalyzed Stille cross-coupling reactions where transmetalation of an R-group bearing electron-withdrawing substituents is desired. While neither toluene nor THF were competent solvents, acetonitrile and *N*-methylpyrrolidone did support slow catalysis.

(3) With appropriate substrates, "ligandless" cross-coupling conditions[27] using $Pd_2(dba)_3$ in DMF could be used. Again, the presence of cocatalytic CuI was essential to catalysis.

(4) CuI was the only competent Cu(I) cocatalyst found; use of CuCl and CuBr resulted in decomposition. Addition of other iodide sources (LiI, I_2, and HI) failed to produce any product, and other halides (LiCl, LiBr) suppressed the cross-coupling.

(5) The apparent rate of cross-coupling seemed to increase as the mol % of CuI was increased; however, the increased rate of formation of the desired quinone product was compromised by an increase in the relative proportion of stannylquinone homocoupling product that formed.

(6) The major competing side-reaction in the palladium-copper cocatalyzed cross-coupling of stannylquinones with aryl and heteroaryl iodides is formation of the symmetrical quinone dimer by oxidative homocoupling of the stannylquinone. This side-product can be effectively suppressed by appropriate choice of reaction conditions, as described below.

Shown in Table I are the results of the palladium-copper-cocatalyzed cross-coupling of three different stannylquinones (two benzoquinones and one naphthoquinone) with aryl and heteroaryl iodides possessing functionality ortho, meta, and para to the iodine. In cases where the cross-coupling proceeded rapidly, 2.5 mol % $Pd_2(dba)_3$ and 50 mol % CuI in DMF open to the air provided effective catalysis for the formation of the substituted quinones. However, when the cross-coupling reaction became slow, two synthetic problems arose. First, catalysis was limited by the lifetime of the "ligandless" catalyst system which, with slower reacting substrates, precipitated Pd-black. In these cases, precipitation of Pd could be inhibited by the use of triphenylarsine as a supporting ligand. Second, the formation of the stannylquinone homocoupling product effectively began to compete with cross-coupling of slower reacting substrates. The palladium-catalyzed oxidative homocoupling of stannylquinones has been studied previously.[22] For this side reaction to compete effectively with the desired cross-coupling, it is presumed the following reaction steps must occur: (1) 2-fold transfer of quinonyl units from the stannylquinone to Pd(II), (2) reductive elimination to the quinone dimer and Pd(0), and (3) reoxidation of Pd(0) to Pd(II). Oxygen from the air as well as the quinone reactants and products themselves could function as oxidants for Pd(0) to Pd(II). Two experimental parameters were routinely adjusted in order to minimize the formation of any quinone dimer. First, to facilitate oxidative addition of the aryl iodide to Pd(0), 2 equiv of aryl iodide were used. This should minimize competitive oxidation of Pd(0) by the above-mentioned alternate oxidants. Second, at the beginning of each reaction, before the stannylquinone was added, the catalyst was allowed to react briefly with the aryl iodide. These two modifications led to successful cross-coupling in most cases, and where the cross-coupling reaction was fast, the reaction could even be conducted open to the air. In cases where the cross-coupling reaction was slow, performing the reaction with the rigorous exclusion of oxygen often improved the yield of quinone cross-coupling product. One drawback to the anaerobic reaction conditions was a significantly reduced reaction rate, which again necessitated the use of triphenylarsine to maintain an active catalyst. From the accumulated results, it appears that the presence of quinone reactants and products in the reaction mixture did not significantly interfere with the desired cross-coupling.

Conclusions

Palladium–copper-cocatalyzed cross-coupling of stannylquinones with various aryl and heteroaryl iodides provides an efficient and straightforward method for the construction of substituted quinones. The direct functionalization of the quinone core via carbon–carbon bond formation without the need for protection–deprotection tactics is noteworthy. Different catalyst–ligand systems were used depending on the substrate. Where possible, "ligandless" conditions ($Pd_2(dibenzylideneacetone)_3$) were best, giving the fastest rate and often the cleanest reaction. For slow reactions added triphenylarsine prolonged the catalyst lifetime. In these slower reactions, a symmetrical biquinone side product from oxidative dimerization of the stannylquinone was formed, but use of an inert atmosphere and rigorously degassed solvents usually eliminated the problem.

The neutral reaction conditions inherent in the palladium-catalyzed cross-coupling of stannylquinones and aryl and heteroaryl iodides should allow the direct introduction of varied functionality on the aryl/heterary1 moiety. In this regard, the other cyclobutenedione-based routes to substituted quinones are more limited, either because of interference from cyclopentenedione formation (4-aryl-alkynylcyclobutenone ring expansions[20]) or because of the strongly basic organolithium reagents needed to introduce substituents to the cyclobutenedione core prior to ring expansion to the quinone.[28-30]

Experimental Section

Materials and Methods. All melting points were performed in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was

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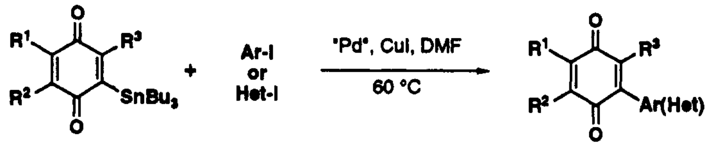
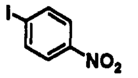
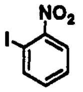
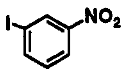
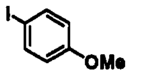
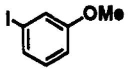
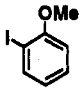
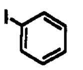
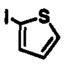
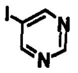
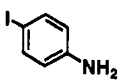
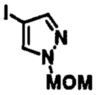
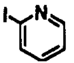
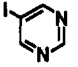
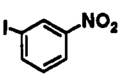
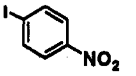
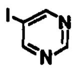
Table I. Palladium–Copper-Cocatalyzed Cross-Coupling of Aryl and Heteroaryl Iodides with Stannylquinones



1 2

entry	R^1, R^2	R^3	aryl or heteroaryl iodide	condns[a]	compd no.	%
1	Me, Me	Me		$Pd_2(dba)_3$, air	**2a**	85
2	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, N_2	**2b**	82
3	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, N_2	**2c**	80
4	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, N_2	**2d**	91
5	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, air[b]	**2e**	67
6	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, air[b]	**2f**	67
7	Me, Me	Me		$Pd_2(dba)_3$, air	**2g**	84
8	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, air	**2h**	61
9	Me, Me	Me		$Pd_2(dba)_3$, argon	**2i**	61
10	Me, Me	Me		$Pd_2(dba)_3$, Ph_3As, N_2	**2j**	59
11	Me, Me	Me		$Pd_2(dba)_3$, argon	**2k**[c]	48
12	Me, Me	Me		$Pd_2(dba)_3$, air	**2l**	76
13	Me, OMe	*n*-Bu		$Pd_2(dba)_3$, air[d]	**2m**	69
14	Me, OMe	*n*-Bu		$Pd_2(dba)_3$, air	**2n**	88
15	benzo	$SiMe_3$		$Pd_2(dba)_3$, air	**2o**	76
16	benzo	$SiMe_3$		$Pd_2(dba)_3$, air	**2p**	49

[a] Typical cross-coupling conditions: 2.5 mol % $Pd_2(dba)_3$, 50 mol % CuI, and 20 mol % Ph_3As (where indicated). [b] Separation of the quinone from dibenzylideneacetone was difficult; purification was achieved by reductive acylation to the hydroquinone diacetate. [c] The unprotected pyrazole did not undergo cross-coupling. [d] Products of the coupling between methyl- and methoxy-substituted stannylquinones and heteroaromatic iodides were unstable; isolation and characterization was accomplished on the corresponding hydroquinone diacetate.

effected with E. Merck silica gel 60F-254 glass-backed plates of 0.25-mm thickness which were visualized with appropriate combinations of UV light, phosphomolybdic acid stain (10% phosphomolybdic acid in ethanol), and anisaldehyde stain (5 mL of *p*-anisaldehyde/95 mL of ethanol/3.5 mL of HOAc/5 mL of concd sulfuric acid). Column chromatography was performed with flash-grade silica gel obtained from EM Science (230–400 mesh). Copper(I) iodide was purified according to a literature procedure.[31] All other reagents and solvents were reagent-grade quality and used as received from the vendor. ^1H NMR spectra were recorded on a G. E. QE 300-MHz spectrometer (frequency = 300.15 MHz) or a Nicolet NT-360 360 MHz spectrometer

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(31) Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1983**, *22*, 101.

(frequency = 361.025). ^{13}C NMR spectra were obtained on the QE 300 (frequency = 75.4808 MHz). Stannylquinones were prepared according to the literature procedure.[21] 2-Iodopyridine was prepared by the method of Baker et al.,[32] and 5-iodopyrimidine was prepared according to the procedure Iversen used for 2-iodothiazole (THF was used instead of diethyl ether as the solvent).[33,34] All other aryl and heteroaryl iodides were purchased from Aldrich and used as received.

General Methods for Cross-Coupling. Procedure A. 2,3,5-Trimethyl-6-(*p*-nitrophenyl)-1,4-benzoquinone, 2a. In a 10-mL round-bottomed flask open to the air was dissolved 0.010 g (0.011 mmol, 2.5 mol %) of $Pd_2(dba)_3$ in 1 mL of DMF and the mixture allowed to stir for 1 min. Then, 1-iodo-4-nitrobenzene (0.23 g, 0.92 mmol, 2 equiv) in 2 mL of DMF was added and the solution was warmed to 60 °C for 2 min. 2,3,5-Trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol) was added in 2 mL of DMF followed immediately by copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %). When the starting material was consumed as judged by TLC (10% Et_2O in hexanes, 30 min to 1 h), the mixture was cooled to room temperature, diluted with 30 mL of Et_2O, washed with two 20-mL portions of 10% aqueous potassium fluoride solution, dried over anhydrous magnesium sulfate, passed through a silica gel plug, and concentrated in vacuo. The resulting yellow solid was purified by gravity chromatography (two sequential columns: SiO_2, 20% Et_2O in hexanes then SiO_2, 10% hexanes in CH_2Cl_2) to give 0.10 g (85%) of a yellow solid. Recrystallization from acetone/methanol/water gave large bright yellow crystals: mp = 138.8–139.4 °C; IR (CCl_4) 2995, 2950, 2895, 1652, 1603, 1528, 1378, 1347, 1274, 1109, 857 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.4, 2 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.1, 185.6, 147.6, 141.9, 141.4, 141.2, 140.6, 140.1, 130.6, 123.2, 14.0, 12.5, 12.4. Anal. Calcd for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.13; H, 4.77; N, 5.34.

Procedure B. 2,3,5-Trimethyl-6-(*p*-methoxyphenyl)-1,4-benzoquinone, 2d. In a 25-mL round-bottomed flask equipped with a side arm nitrogen inlet were combined $Pd_2(dba)_3$ (0.026 g, 0.028 mmol, 2.5 mol %) and triphenylarsine (0.070 g, 0.23 mmol, 20 mol %) in 2 mL of degassed DMF and the mixture allowed to stir for 1 min under a nitrogen purge. Then 1-iodo-4-methoxybenzene (0.53 g, 2.3 mmol, 2 equiv) in 4 mL of DMF was added. The reaction flask was heated to 60 °C for 2 min, and then 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.50 g, 1.1 mmol) in 3 mL of degassed DMF was added followed by copper(I) iodide (0.11 g, 0.57 mmol, 50 mol %). The reaction was followed by TLC (10% Et_2O in hexanes), and when the starting material was consumed (3–4 h) the mixture was cooled to room temperature, diluted with 50 mL of Et_2O, washed with two 40-mL portions of 10% aqueous potassium fluoride solution, dried over anhydrous magnesium sulfate, passed through a silica gel plug, and concentrated in vacuo. The resulting orange semisolid was purified by gravity chromatography (SiO_2, 10% EtOAc in hexanes, material was adsorbed onto silica and introduced to the head of a slurry-packed column) to give the desired product in 91% yield (0.27 g). Recrystallization from acetone/methanol/water gave large bright orange crystals: mp = 67–68 °C; IR (CH_2Cl_2) 3060, 2964, 2840, 1648, 1607, 1513, 1376, 1293, 1274, 1260, 1250, 1179, 1111, 1092, 872, 832; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J = 8.6 Hz, 2 H), 6.94 (d, J = 8.6 Hz, 2 H), 3.83 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.1, 186.8, 159.5, 143.0, 140.7, 140.6, 140.4, 131.0, 125.5, 113.4, 55.2, 14.1, 12.4 (two resolved peaks at 12.43 and 12.39). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.83; H, 6.31.

2,3,5-Trimethyl-6-(*o*-nitrophenyl)-1,4-benzoquinone, 2b. Using procedure B above, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), triphenylarsine (0.03 g, 0.1 mmol, 20 mol %), 1-iodo-2-nitrobenzene (0.23 g, 0.90 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.2 g, 0.45 mmol) and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of degassed DMF under nitrogen. After workup a yellow semisolid was obtained which was purified by gravity chromatography (20% Et_2O in hexanes) to give 0.15 g (82%) of a ruddy yellow solid. Recrystallization from Et_2O/hexanes gave bright yellow crystals: mp = 100–101 °C; IR (CH_2Cl_2) 3062, 1650, 1530, 1378, 1351, 1275, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 8.21 (d, J = 8.2 Hz, 1 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.23 (d, J = 8.3 Hz, 1 H), 2.08 (s, 3 H), 2.02 (s, 3 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.1, 185.0, 148.1, 142.0, 141.3, 140.6, 139.9, 133.6, 131.5, 129.7, 129.5, 124.6, 13.6, 12.2, 12.0. Anal. Calcd for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83. Found: C, 66.21; H, 4.89.

2,3,5-Trimethyl-6-(*m*-nitrophenyl)-1,4-benzoquinone, 2c. Using procedure B above, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), triphenylarsine (0.03 g, 0.1 mmol, 20 mol %), 1-iodo-3-nitrobenzene (0.23 g, 0.90 mmol, 2 equiv) 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol), and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of degassed DMF under nitrogen. After workup a yellow semisolid was obtained which was purified by gravity chromatography (SiO_2, 10% Et_2O in hexanes followed by a second column: SiO_2, 20% hexanes in CH_2Cl_2) to give 0.99 g (80%) of the desired product. Recrystallization (minimum acetone/50% methanol:water) gave bright yellow crystals: mp = 131.1–131.8 °C; IR (CH_2Cl_2) 3060, 2975, 2950, 2920, 1650, 1534, 1354, 1378 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (dd, J = 8.0 and 1.4 Hz, 1 H), 8.01 (s, 1 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.2, 185.7, 147.9, 142.1, 141.2, 141.1, 140.5, 134.9, 135.6, 129.0, 124.6, 123.4, 14.0, 12.5, 12.4. Anal. Calcd for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.30, H, 4.87; N, 5.12.

2,3,5-Trimethyl-6-phenyl-1,4-benzoquinone, 2g. Using procedure A above, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), iodobenzene (0.11 mL, 0.90 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol), and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of DMF. Purification by gravity chromatography (25% Et_2O in hexanes) gave a yellow solid in 84% yield (0.087 g): mp = 81.0–81.7 °C; IR ($CDCl_3$) 2962, 1648, 1378, 1302, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4 (m, 3 H), 7.18 (dd, J = 1.6 and 7.6 Hz, 2 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 1.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.0, 186.5, 143.4, 141.0, 140.6, 140.5, 133.4, 129.3, 128.2, 127.9, 13.9, 12.4 (two coincident methyls). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.62; H, 6.26.

2,3,5-Trimethyl-6-(2-thienyl)-1,4-benzoquinone, 2h. Using procedure B above (open to the air), $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), triphenylarsine (0.028 g, 0.09 mmol, 20 mol %), 1-iodo-3-nitrobenzene (0.19 g, 0.90 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol), and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of DMF open to the air. After workup a red semisolid was obtained which was purified by gravity chromatography (SiO_2, 10% Et_2O in hexanes) to give 65.1 mg (61%) of a red/orange product. Recrystallization from Et_2O/hexane gave small red/orange plates: mp = 55.8–57.2 °C; IR (CH_2Cl_2) 3130, 3062, 2929, 2858, 1650, 1600, 1422, 1375, 1362, 1293, 1270, 1090, 911, 868, 855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (dd, J = 5.1 and 1.1 Hz, 1 H), 7.12 (m, 2 H), 2.18 (s, 3 H), 2.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.3, 186.0, 140.9, 140.6, 140.4, 136.6, 133.0, 130.5, 129.3, 126.3, 14.7, 12.5 (two resolved peaks at 12.53 and 12.57). Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.15; H, 5.24; S, 13.89.

2,3,6-Trimethyl-5-(5-pyrimidyl)-1,4-benzoquinone, 2i. Using procedure A (under argon), $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), 5-iodopyrimidine (0.19 g, 0.92 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol), and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of DMF. Purification by flash chromatography (SiO_2, 30% Et_2O in hexanes) gave 0.063 g (61%) of a yellow solid. Recrystallization from cyclohexane/acetone gave fine yellow crystals: mp = 143.0–143.2 °C; IR (CH_2Cl_2) 3095, 2964, 2930, 1650, 1623, 1576, 1551, 1416, 1378, 1304, 1283, 1270, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.19 (s, 1 H), 8.54 (s, 2 H), 2.07 (s, 3 H), 2.04 (s, 1 H), 1.99 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.6, 185.3, 158.1, 157.1, 142.9, 141.5, 140.5, 136.8, 127.4, 14.1,

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12.5, 12.4. Anal. Calcd for $C_{13}H_{12}O_2N_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.64, H, 5.48; N, 12.08.

2,3,5-Trimethyl-6-(*p*-aminophenyl)-1,4-benzoquinone, 2j. Using procedure B above, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), triphenylarsine (0.03, 0.1 mmol, 20 mol %), 1-iodo-4-aminobenzene (0.20 g, 0.9 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.2 g, 0.45 mmol), and copper(I) iodide (0.043 g, 0.23 mmol, 50 mol %) were combined in 5 mL of degassed DMF under nitrogen. Workup: when consumption of starting material was verified by TLC, the mixture was cooled to room temperature, diluted with 30 mL of Et_2O, washed with two 20-mL portions of 10% aqueous potassium fluoride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting dark purple semisolid was introduced onto a 3.8-cm × 16-cm SiO_2 column with Et_2O, and the column was then washed with 10% Et_2O in hexanes to remove the side products. Finally the eluant was changed to 25% Et_2O in hexanes to wash off the dark red product. After solvent removal, the pure product was obtained in 59% yield (0.065 g) as a dark purple solid: mp = 122.0–123.5 °C; IR ($CDCl_3$) 3406, 2927, 1646, 1623, 1517, 1376, 1291, 1272, 830, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 8.4 Hz, 2 H), 3.84 (br s, 2 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.3, 187.0, 146.8, 143.3, 140.6, 140.4, 140.0, 131.1, 122.9, 114.3, 14.2, 12.5, 12.4. Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.51; H, 6.30, N, 5.79.

2,3,6-Trimethyl-5-(4-(1-methoxymethyl)pyrazolyl)-1,4-benzoquinone, 2k. 4-Iodo-1-(methoxymethyl)pyrazole was prepared in the following manner. In a 100-mL round-bottomed flask under argon was suspended NaH (0.25 g, 10 mmol) in 40 mL of dry Et_2O and the mixture cooled in an ice bath. Next, 4-iodopyrazole (2.0 g, 10 mmol) was dissolved in 20 mL of dry Et_2O and added dropwise to the stirred NaH suspension (H_2 evolution). The solution was stirred at 0 °C for 15 min, and then methyl chloromethyl ether, MOMCl (0.8 mL, 10 mmol), was added all at once via syringe with formation of a white precipitate. The mixture was stirred at 0 °C for 5 min and then warmed to room temperature and stirred a further 15 min. Finally the mixture was diluted with 100 mL of Et_2O, washed with three 100-mL portions of water, dried over Na_2SO_4, and condensed in vacuo. The desired product was obtained as a yellow oil in 83% yield (0.056 g): IR (CH_2Cl_2) 3133, 3052, 3004, 2985, 2939, 2834, 1710, 1607, 1513, 1455, 1424, 1372, 1308, 1272, 1258, 1194, 1167, 1106, 1032, 978, 944, 918, 855, 807 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (s, 1 H), 7.55 (s, 1 H), 5.36 (s, 2 H), 3.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 134.1, 81.9, 58.2, 56.8. Anal. Calcd for $C_5H_7ON_2I$: C, 25.23; H, 2.96; N, 11.77. Found: C, 25.33; H, 2.96; N, 11.78.

Using procedure A (under argon), $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), 4-iodo-1-(methoxymethyl)pyrazole (0.22 g, 0.92 mmol, 2 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.20 g, 0.45 mmol), and copper(I) iodide (0.017 g, 0.09 mmol, 20 mol %) were combined in 5 mL of DMF. Purification by flash chromatography (SiO_2, 15% Et_2O in hexanes) gave 0.056 g of a yellow-orange amorphous solid in 48% yield: mp = 78–79 °C; IR (CH_2Cl_2) 3062, 2937, 1648, 1615, 1554, 1434, 1378, 1333, 1293, 1270, 1160, 1108, 1096, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1 H), 7.71 (s, 1 H), 5.42 (s, 2 H), 3.37 (s, 3 H), 2.18 (s, 3 H), 2.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.5, 186.4, 141.5, 140.7, 140.4, 138.9, 134.4, 132.0, 114.4, 82.1, 56.9, 14.4, 12.6, 12.5. Anal. Calcd for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.70; H, 6.28; N, 10.55.

2,3,6-Trimethyl-5-(1-pyridyl)-1,4-benzoquinone, 2l. Using procedure A, as above, $Pd_2(dba)_3$ (0.026 g, 0.028 mmol, 2.5 mol %), 2-iodopyridine (0.30 g, 1.5 mmol, 1.3 equiv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.50 g, 1.1 mmol), and copper(I) iodide (0.11, g, 0.57 mmol, 50 mol %) were combined in 10 mL of DMF. Purification by flash chromatography (25% Et_2O in hexanes) gave 0.20 g (76%) of a brown-yellow solid. Sublimation at 75 °C and 4.5 mm Hg gave dark yellow needles: mp = 61.1–61.3 °C; IR (CH_2Cl_2) 3066, 3047, 2980, 2940, 2929, 1650, 1470, 1430, 1376, 1349, 1289, 1270, 1260, 1200 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz), δ 8.64 (d, J = 5.5 Hz, 1 H), 7.75 (dt, J = 7.7 and 1.5 Hz, 1 H), 7.28 (dd, J = 7.5 and 4.9 Hz, 1 H), 7.18 (d, J = 7.8 Hz, 1 H), 2.05 (s, 3 H), 2.01 (s, 3 H), 1.87 (s, 3 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 187.9, 186.3, 153.1, 149.2, 141.8, 142.0, 140.7, 140.3, 135.7, 125.0, 122.8, 13.0, 12.1, 12.0. Anal. Calcd for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77, N, 6.16. Found: C, 73.93; H, 5.83; N, 6.12.

2-Butyl-3-(*m*-nitrophenyl)-5-methoxy-6-methyl-1,4-benzoquinone, 2n. Using procedure A, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), 1-iodo-3-nitrobenzene (0.23 g, 0.9 mmol, 2 equiv), 2-*n*-butyl-5-methoxy-6-methyl-3-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.25 g, 0.46 mmol), and copper(I) iodide (0.044 g, 0.23 mmol, 50 mol %) were combined in 5 mL of DMF. Purification by flash chromatography (10% Et_2O in hexanes) followed by gravity chromatography (CH_2Cl_2) gave 0.13 g (88%) of an orange semi-solid: IR (CH_2Cl_2) 3062, 2964, 2935, 2875, 1650, 1607, 1534, 1449, 1353, 1287, 1262, 1192, 1138, 1102, 911, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 8.28 (d, J = 8.7 Hz, 1 H), 8.05 (s, 1 H), 7.63 (t, J = 7.9 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 4.01 (s, 3 H), 2.31 (apparent dd, J = 8.2, and 7.3 Hz, 2 H), 2.02 (s, 3 H), 1.35 (m, 2 H), 1.21 (sex, J = 7.2 Hz, 2 H), 0.76 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.6, 182.4, 155.0, 148.0, 146.6, 139.6, 135.5, 134.5, 129.2, 124.4 (two resolved peaks at 124.41 and 124.42), 123.4, 61.0, 31.9, 28.1, 22.9, 13.5, 8.9. Anal. Calcd for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.74; H, 5.86; N, 4.18.

2-(Trimethylsilyl)-3-(*p*-nitrophenyl)-1,4-naphthoquinone, 2o. Using procedure A, above, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), 1-iodo-4-nitrobenzene (0.25 g, 0.88 mmol, 2 equiv), 2-(trimethylsilyl)-3-(tri-*n*-butylstannyl)-1,4-naphthoquinone (0.25 g, 0.44 mmol), and copper(I) iodide (0.042 g, 0.22 mmol, 50 mol %) were combined in 5 mL of DMF. Purification by flash chromatography (SiO_2, 10% Et_2O in hexanes followed by a second column: SiO_2, 40% hexanes in CH_2Cl_2) gave 0.12 g (76%) of the desired product as a mustard yellow solid. Recrystallization from acetone/water gave dark yellow crystals: mp = 201–203 °C; IR (CH_2Cl_2) 3066, 2958, 1663, 1601, 1524, 1351, 1318, 1285, 1260, 1125, 1063, 1023, 884, 861, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, J = 8.5, 2 H), 8.06 (apparent dt, 2 H), 7.75 (m, 2 H), 7.40 (d, J = 8.5, 2 H), –0.028 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.9, 183.3, 154.5, 152.4, 148.0, 142.3, 134.0, 133.7, 133.0, 131.6, 130.6, 126.5, 126.3, 122.9, 0.6. Anal. Calcd for $C_{19}H_{17}O_4SiN$: C, 64.94; H, 4.88; N, 3.99. Found: C, 64.97; H, 4.89; N, 3.98.

2-(Trimethylsilyl)-3-(5-pyrimidyl)-1,4-naphthoquinone, 2p. Using procedure A, $Pd_2(dba)_3$ (0.010 g, 0.011 mmol, 2.5 mol %), 5-iodopyrimidine (0.18 g, 0.87 mmol, 2 equiv), 2-(trimethylsilyl)-3-(tri-*n*-butylstannyl)-1,4-naphthoquinone (0.25 g, 0.44 mmol), and copper(I) iodide (0.042 g, 0.22 mmol, 50 mol %) were combined in 5 mL of DMF. Purification by flash chromatography (SiO_2, 30% Et_2O in hexanes) gave a brown-red solid in 49% yield (0.067 g). Recrystallization from methanol/water gave light brown crystals: mp = 97–99 °C; IR (CH_2Cl_2) 3052, 2983, 2958, 2920, 1663, 1596, 1580, 1553, 1414, 1322, 1285, 1270, 1138, 1065, 878, 851 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.27 (s, 1 H), 8.62 (s, 2 H), 8.08 (m, 2 H), 7.77 (m, 2 H), 0.019 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.4, 183.0, 158.5, 156.6, 154.1, 149.9, 134.2, 133.8, 133.0, 131.4, 129.8, 126.6, 126.4, 1.0. Anal. Calcd for $C_{17}H_{16}O_2N_2Si$: C, 66.21; H, 5.23; N, 9.08. Found: C, 66.30; H, 5.28; N, 8.85.

General Procedure for Cross-Coupling and Reductive Acylation.[35] **2,3,5-Trimethyl-6-(*m*-methoxyphenyl)-1,4-diacetoxybenzene, 2e.** In a 25-mL round-bottomed flask open to the air were combined $Pd_2(dba)_3$ (0.030 g, 0.33 mmol, 2.5 mol %) and triphenylarsine (0.070 g, 0.23 mmol, 20 mol %) in 2 mL of DMF. The solution was stirred for 1 min until the purple color was discharged. 3-Iodoanisole (0.53 g, 4.3 mmol, 2 equiv) was then added, and the mixture was heated for 2 min at 60 °C. To the warm solution were added 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.50 g, 1.1 mmol) and copper(I) iodide (0.11 g, 0.57 mmol, 50 mol %), and the total volume of DMF was brought to 8 mL. The reaction was monitored by TLC (10% Et_2O in hexanes) for disappearance of stannylquinone. When the reaction was complete, the solution was diluted with 40 mL of Et_2O and washed with two 20-mL portions of 10% aqueous KF. The resulting mixture was passed through a SiO_2 plug and

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condensed in vacuo. Reductive acylation was carried out in a 10-mL round-bottomed flask fitted with a reflux condenser under nitrogen. In this vessel the crude product from above was dissolved in 2 mL of acetic anhydride, and NaOAc (0.037 g, 4.5 mmol, 0.4 equiv) and zinc powder (0.11 g, 1.7 mmol, 1.5 equiv) were added. The mixture was gently heated until most of the color was discharged and then brought to reflux for 1 min to complete the reaction. The reaction vessel was cooled slightly, 2 mL of glacial acetic acid was added, and the mixture was again refluxed for 1 min. After 1 min the mixture was cooled to room temperature and the liquid removed with a pipette. The remaining solids ($Zn(OAc)_2$ and Zn) were washed with three 2-mL portions of glacial acetic acid, and the combined washings were dissolved in CH_2Cl_2. The crude mixture was neutralized with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and condensed in vacuo. Purification by gravity chromatography (SiO_2, 4:15 EtOAc/hexane) gave a sticky clear residue in 67% yield (0.26 g). IR (CH_2Cl_2) 3064, 3006, 2988, 2939, 2838, 1758, 1601, 1580, 1493, 1466, 1434, 1370, 1287, 1202, 1148, 1082, 1044, 1019, 830, 561 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz), δ 7.31 (t, J = 7.9 Hz, 1 H), 6.92 (dd, J = 8.2 and 2.7 Hz, 1 H), 6.65 (s, broad resolving into two peaks at 6.7 and 6.7 when heated to 50 °C, 2 H), 3.76 (s, 3 H), 2.31 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.84 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 169.0, 159.3, 145.9, 144.7, 138.0, 133.3, 129.2, 129.1, 127.7, 127.1, 121.9, 114.7, 113.2, 55.2, 20.5, 20.2, 14.0, 13.3, 13.1. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.28, H, 6.44.

The following compounds were prepared in an analogous manner to **2e**.

2,3,5-Trimethyl-6-(*o*-methoxyphenyl)-1,4-diacetoxybenzene, 2f. $Pd_2(dba)_3$ (0.030 g, 0.033 mmol, 2.5 mol %), triphenylarsine (0.07 g, 0.02 mmol, 20 mol %), 2-iodoanisole (0.53 g, 2.2 mmol, 2 equv), 2,3,5-trimethyl-6-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.50 g, 1.1 mmol), and copper(I) iodide (0.11, 0.57 mmol, 50 mol %) were combined in 10 mL of DMF open to the air. After workup the crude orange product was dissolved in 2 mL of acetic anhydride to which was added zinc powder (0.11 g, 1.7 mmol, 1.5 equiv) and NaOAc (0.037 g, 4.5 mmol, 0.5 equiv). The product was purified by gravity chromatography (SiO_2, 4:15 EtOAc/hexane) to give 0.26 g (67%) of a white amorphous solid: IR (CH_2Cl_2) 3064, 2999, 2975, 2935, 2840, 1758, 1713, 1602, 1582, 1499, 1466, 1436, 1370, 1246, 1206, 1158, 1113, 1081, 1050, 1026, 830, 560 cm^{-1}; ^1H NMR (DMSO, 300 MHz), δ 7.33 (dt, J = 8.3 and 0.9 Hz, 1 H), 7.05 (d, J = 8.2, 1 H), 6.94 (t, J = 7.3, 1 H), 6.84 (d, J = 7.1, 1 H, broad), 3.62 (s, 3 H), 2.31 (s, 3 H), 2.02 (s, 3 H), 1.97 (s, 3 H), 1.77 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9 (two coincident acetate carbonyls), 157.0, 145.8, 145.0, 131.1 (broad), 130.0, 129.1 (two resolved peaks at 129.10 and 129.14), 127.6, 128.0, 125.2, 120.2, 110.8, 55.5, 20.5, 20.2, 13.8, 13.3, 13.4. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.02; H, 6.51.

2-Butyl-3-(5-pyrimidyl)-5-methoxy-6-methyl-1,4-diacetoxybenzene, 2m. Using the procedure stated above for 2,3,5-trimethyl-6-(*m*-methoxyphenyl)-1,4-diacetoxybenzene (without added triphenylarsine), $Pd_2(dba)_3$ (0.021 g, 0.023 mmol, 2.5 mol %), 5-iodopyrimidine (0.38 g, 1.8 mmol, 2 equiv), 2-*n*-butyl-5-methoxy-6-methyl-3-(tri-*n*-butylstannyl)-1,4-benzoquinone (0.50 g, 0.92 mmol), and copper(I) iodide (0.090 g, 0.47 mmol, 50 mol %) were combined in 10 mL of DMF open to the air. After workup the crude orange product was dissolved in 3 mL of acetic anhydride to which was added zinc powder (0.090 g, 1.4 mmol, 1.5 equiv) and NaOAc (0.038 g, 4.6 mmol, 0.5 equiv). The product was purified by gravity chromatography (SiO_2, 45% EtOAc in hexanes) to give 0.21 g (69%) of a sticky clear amorphous solid: IR (CH_2Cl_2) 3049, 2964, 2934, 2875, 1766, 1553, 1455, 1408, 1372, 1343, 1274, 1266, 1214, 1196, 1175, 1109, 1054, 1046, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.21 (s, 1 H), 8.6 (s, 2 H), 3.75 (s, 3 H), 2.34 (s, 3 H), 2.19 (t, J = 8.0 Hz, 2 H), 2.12 (s, 3 H), 1.98 (s, 3 H), 1.25 (m, 2 H), 1.12 (q, J = 7.1, 2 H), 0.72 (t, J = 7.2, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 168.7, 157.9, 157.2, 148.9, 146.4, 140.1, 129.9, 130.1, 127.0, 126.8, 61.0, 32.0, 27.7, 22.7, 20.48, 20.1, 13.5, 10.3. Anal. Calcd for $C_{20}H_{24}O_5N_2$: C, 64.50; N, 7.52. Found: C, 64.63; H, 6.47; N, 7.44.

Acknowledgment. This investigation was supported by Grant No. CA40157, awarded by the National Cancer Institute, DHHS. The authors thank Mr. Sensuke Ogoshi of Osaka University for his involvement in the early stages of this project. We acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health, S10-RR-02478, and a 300-MHz NMR and a 360-MHz NMR purchased through funding from the National Science Foundation, NSF CHE-85-16614 and NSF CHE-8206103, respectively.