4,4′-Bi(cyclobutene-1,2-diones): Bisquaryls

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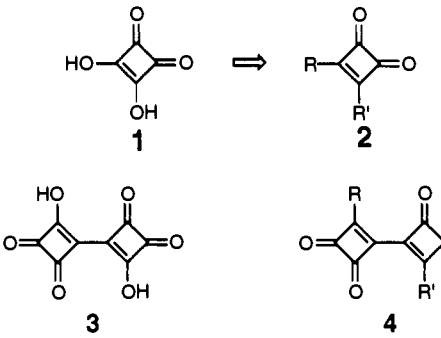
Abstract: 4,4′-Bi(cyclobutene-1,2-diones), novel compounds derived from squaric acid, here named bisquaryls, were prepared for the first time either by the palladium-catalyzed oxidative dimerization of (tri-*n*-butylstannyl)cyclobutene-1,2-diones (providing symmetrically substituted bisquaryls) or by a palladium–copper cocatalyzed cross-coupling of 3-substituted-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones with 3-halo-4-substituted-3-cyclobutene-1,2-diones (providing a route to unsymmetrically substituted bisquaryls). The novel parent bisquaric acid is a very strong Brønsted acid that apparently fully ionizes on dissolution; only one pK_a value ($pK_2 = -4.49$) was observed.

Introduction

Since its synthesis was first reported over 30 years ago,[2,3] squaric acid, **1**, and the cyclobutene-1,2-diones, **2**, structurally related or synthetically derived from it, have been the subject of numerous articles and patents. These detail novel reactions,[4-12] biologically interesting properties,[13-27] and applications to advanced materials.[28-40] Just as the opportunities for interesting chemistry based on arene transformations broaden on progressing from monoarenes to biaryls, one could anticipate a wealth of novel chemistry ensuing from the development of the analogous dimers, **3** and **4**, derived from squaric acid and its cyclobutene-1,2-dione derivatives, respectively. Documented herein is a simple method for the synthesis of bisquaric acid, **3**, and symmetrical and unsymmetrical 4,4′-bi(cyclobutene-1,2-diones), **4**, here named bisquaryls in order to emphasize their relationship to biaryls.



Results and Discussion

Preparation of Stannylcyclobutene-1,2-diones. A straightforward synthesis of some *symmetrically* substituted 4,4′-bi(cyclobutene-1,2-diones) emerges from the ready access to 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones, **5–7**, and the known formation of dienes by the palladium-catalyzed homocoupling of alkenylstannanes.[41,42] Amino-substituted (tri-*n*-butylstannyl)-cyclobutene-1,2-diones, **6**, were prepared by treatment of 3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **5**,[43] with the appropriate primary or secondary amine in 2-propanol. For example, 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e**, was generated in 83% yield by treating 3-(1-methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione[43] with 1 equiv. of piperidine in 2-propanol at room

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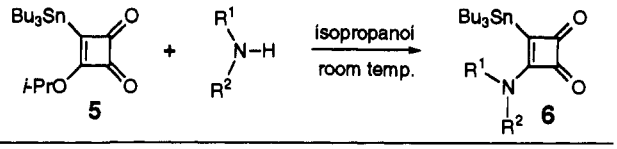
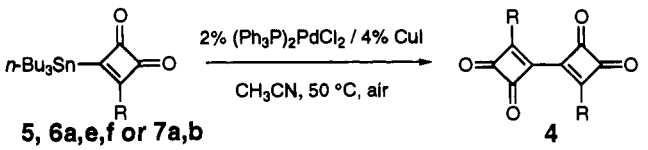
Table I. Preparation of (Tri-*n*-butylstannyl)squaramides



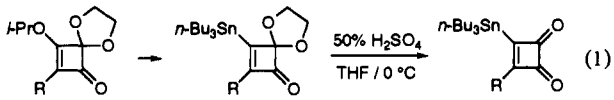
R^1	R^2	product	yield (%)
H	H	**6a**	85
H	Me	**6b**	83
H	*n*-Pr	**6c**	80
H	*i*-Pr	**6d**	80
$-(CH_2)_5-$		**6e**	83
$-(CH_2)_2O(CH_2)_2-$		**6f**	76

Table II. Palladium-Catalyzed Oxidative Dimerization of 3-(Tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones



entry	starting mat.	R	product	yield (%)
1	**6a**	NH_2	**4a**	83
2	**6e**	1-piperidinyl	**4b**	60
3	**6f**	1-morpholinyl	**4c**	63
4	**7a**	Me	**4d**	---
5	**7b**	Ph	**4e**	---
6	**5**	O-*i*-Pr	**4f**	---

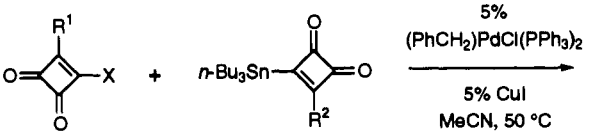
temperature.[44] The other nitrogen-containing analogs were prepared similarly (Table I). 3-Methyl-4(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7a**, and 3-phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7b**, were readily prepared by hydrolysis of the corresponding monoacetals, which themselves were prepared following established procedures (eq 1).[43,45]



7a, R = Me
7b, R = Ph

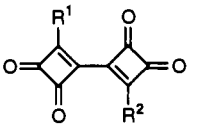
Symmetrical Bisquaryls. The results of the homocoupling of (tri-*n*-butylstannyl)cyclobutene-1,2-diones **5**, **6a,e,f**, and **7a,b** are listed in Table II. The reaction of 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e**, in acetonitrile with a catalyst system composed of 2 mol % of bis(triphenylphosphine)-palladium dichloride and 4 mol % of CuI gave **4b** in 60% yield. Using the same conditions, the highly insoluble parent bisquaramide **4a** and the analogous 1-morpholinyl derivative **4c** were prepared in good yields from 3-amino-(4-tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6a**, and 3-(1-morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6f**, respectively. An attempt to homocouple 3-methyl-(4-tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7a**, failed to give **4d**. The analogous phenyl derivative, 4,4'-bi(3-phenyl-3-cyclobutene-1,2-dione), **4e**, could be prepared in crude form from **7b**, but attempted purification was not successful. 3-Isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **5**, did not transform cleanly into 4,4'-bi(3-isopropoxy-3-cyclobutene-1,2-dione), **4f**, under the palladium-catalyzed homocoupling conditions. However, both **4f** and the phenyl-substituted bisquaryl, **4e**, were prepared and purified using the palladium-catalyzed cross-coupling method described below.

Table III. Unsymmetrical Bisquaryls by Palladium-Catalyzed Cross-Coupling



8c, R^1 = O*i*-Pr, X = Cl
8d, R^1 = Ph, X = Br

5, 6, 7b



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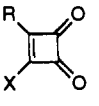
entry	reactants	R^1	R^2	product	yield (%)
1	**8c + 6a**	O-*i*-Pr	NH_2	**9a**	50
2	**8c + 6b**	O-*i*-Pr	NHMe	**9b**	47
3	**8c + 6c**	O-*i*-Pr	NH-*n*-Pr	**9c**	64
4	**8c + 6d**	O-*i*-Pr	NH-*i*-Pr	**9d**	91
5	**8c + 6e**	O-*i*-Pr	NC_5H_{10}	**9e**	60
6	**8d + 6d**	Ph	NH-*i*-Pr	**9f**	90
7	**8d + 6e**	Ph	NC_5H_{10}	**9g**	52
8	**8d + 7b**	Ph	Ph	**4e**	78
9	**8c + 5**	O-*i*-Pr	O-*i*-Pr	**4f**	84

The palladium-catalyzed homocoupling reaction did not function in the absence of either CuI or air. The requirement for cocatalytic CuI adds this reaction to a growing list of organotin, organoboron, and organozinc cross-coupling protocols that require or proceed best in the presence of cocatalytic CuI.[43,44,46-54] The choice of the Pd catalyst and the presence of supporting ligands made little difference in the reaction; effective catalysis was observed with either Pd(0) or Pd(II) sources and in the presence or absence of phosphine ligands. On the other hand, the choice of solvent was quite important. The observed rate of the reaction was highly dependent on the polarity of the solvent; the rates of reaction followed the order *N*-methylpyrrolidone = DMF > CH_3CN > THF ≫ benzene = dioxane. Acetonitrile was the most convenient solvent to use, since the reaction proceeded at a reasonable rate and an acetonitrile/hexane partition could be used after the reaction to remove tri-*n*-butyltin residues.

Unsymmetrical Bisquaryls. By reacting 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones; **5**, **6**, or **7b**, with 3-halo-3-cyclobutene-1,2-diones, **8**, under conditions previously established for palladium-



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a: R = Me, X = Cl
b: R = Me, X = Br
c: R = O*i*-Pr, X = Cl
d: R = Ph, X = Br

catalyzed cross-coupling of simpler organostannanes with 3-halocyclobutene-1,2-diones[55] and of stannylcyclobutene-1,2-diones with various organic halides,[43] it proved possible to prepare unsymmetrically substituted 4,4'-bi(cyclobutene-1,2-diones) as well as several symmetrical bisquaryls not obtainable under the homocoupling procedure described above (Table III). 3-Halocyclobutene-1,2-diones **8a–c** were prepared following previously established procedures. 3-Chloro-4-methyl-3-cyclobutene-1,2-

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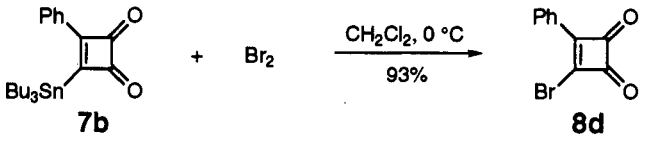
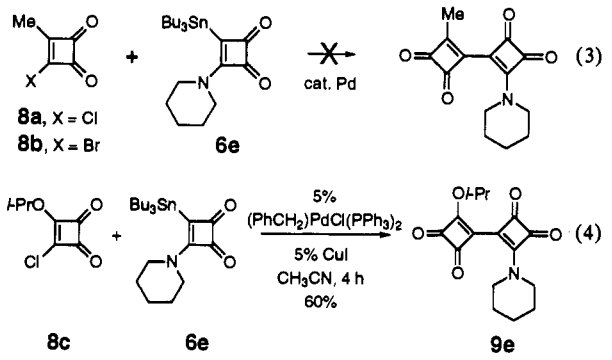
dione, **8a**, was made by chlorination of 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione with oxalyl chloride and catalytic DMF.[56] Likewise, 3-bromo-4-methyl-3-cyclobutene-1,2-dione, **8b**, was generated by DMF-catalyzed reaction of 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione with oxalyl bromide.[55] 3-Chloro-4-isopropoxy-3-cyclobutene-1,2-dione, **8c**,[55] was generated by addition of 2-propanol to dichlorocyclobutene-1,2-dione, following the procedure of Schmidt.[57] Attempts to synthesize **8d** by applying the oxalyl bromide method to 3-hydroxy-4-phenyl-3-cyclobutene-1,2-dione failed. However, compound **8d** was trivially prepared in 93% yield from the reaction of **7b** with bromine at 0 °C in methylene chloride (eq 2).



(2)

Although 3-halocyclobutene-1,2-diones **8a** and **8b** were good cross-coupling partners for the preparation of substituted cyclobutene-1,2-diones,[55] these same reactants did not provide stable unsymmetrical bisquaryls on attempted cross-coupling with stannylcyclobutene-1,2-dione **6e** (eq 3). However, in the presence of 5% $(PhCH_2)PdCl(PPh_3)_2$ and 5% CuI, 3-chloro-4-(isopropoxy)-3-cyclobutene-1,2-dione, **8c**, underwent cross coupling with 3-(1-piperidinyl)-4-tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e**, in CH_3CN to give bisquaryl **9e** in 60% yield (eq 4).



This cross-coupling reaction was successfully extended to the preparation of other bisquaryls derived from 3-chloro-4-(isopropoxy)-3-cyclobutene-1,2-dione, **8c**, and (tri-*n*-butylstannyl)-cyclobutene-1,2-diones bearing either an oxygen, **5**, or nitrogen, **6**, substituent (Table III). Cross coupling with 3-bromo-4-phenyl-3-cyclobutene-1,2-dione, **8d**, also led to isolable products (Table III, entries 6 and 7). Furthermore, by appropriate choice of reaction partners, the cross-coupling protocol also provided a route to symmetrically substituted bisquaryls which were not isolable using the homocoupling conditions described above (Table III, entries 8 and 9).

The success of the cross-coupling of 3-(isopropoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **5**, and its nitrogen-containing analogs **6** with halocyclobutene-1,2-diones **8c** and **8d** prompted an exploration of the reaction of alkyl-substituted stannylcyclobutene-1,2-diones with these compounds. Unfortunately, no desired products were isolable using 3-methyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7a**, with either **8c** or **8d**. Likewise, attempts to synthesize these compounds by the reaction of alkyl-substituted halocyclobutene-1,2-diones such as **8a** and **8b** with stannylcyclobutene-1,2-diones failed.

4,4′-Bi(3-hydroxy-3-cyclobutene-1,2-dione), Bisquaric Acid, 3. The parent bisquaric acid, 4,4′-bi(3-hydroxy-3-cyclobutene-1,2-dione), **3**, was prepared by hydrolysis of 4,4′-bi(3-isopropoxy-3-cyclobutene-1,2-dione), **4f**, which itself was easily synthesized by the palladium-catalyzed cross-coupling of **5** with **8c**. Treatment of 4,4′-bi(3-isopropoxy-3-cyclobutene-1,2-dione), **4f**, dissolved in a minimum amount of THF, with concentrated HCl (approximately 0.2 mL for 400 mg of **4f**) at room temperature within 3 h led to hydrolysis and precipitation of bisquaric acid in good yield as a bright yellow solid (eq 5). This material was insoluble

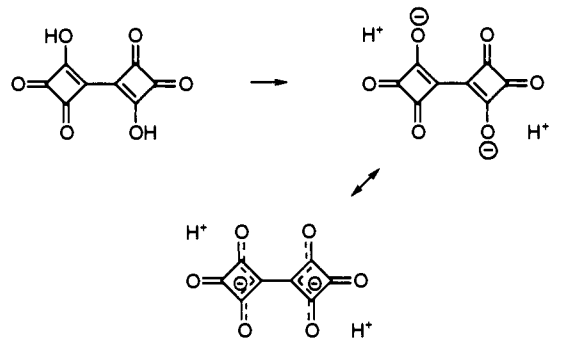
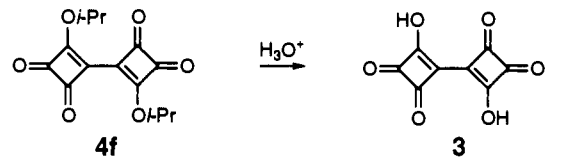


Figure 1. Ionization and resonance delocalization of bisquaric acid in solution.



in nearly all solvents except water and DMSO. The solid did not melt at temperatures up to 270 °C, and decomposition was not observed, although a slight change in color from yellow to light brown occurred. The highly insoluble yellow solid, which could not be sublimed, did not give a satisfactory high-resolution mass spectrum (no vaporization up to 500 °C). The bisquaric acid that precipitated on hydrolysis of **4f** in THF contained 0.25 mol of tightly bound H_2O, as evidenced by combustion analysis. Drying at 90 °C under vacuum for 18 h did not remove the water. The infrared spectrum (KBr pellet) of bisquaric acid showed ν_{CO} = 1837 and 1773 cm^{-1} and ν_{OH} absorptions at 3573 and 3431(br) cm^{-1}, as expected for bound water and typical hydroxyl groups. An unusual broad absorption at 2428 cm^{-1} was also seen, indicative of strong hydrogen bonding (=O···H—O). Similar absorptions were previously documented in the IR spectra of squaric acid[2] and moniliformin.[58] The insolubility of bisquaric acid and the appearance of the 2428-cm^{-1} band in the infrared spectrum taken in KBr are consistent with a solid-state structure where polymerization through strong hydrogen bonding has taken place (see below).

An infrared spectrum of bisquaric acid dissolved in DMSO showed a broad absorption at 3478 cm^{-1} and sharp absorptions at 1721 and 1619 cm^{-1}. The ^{13}C NMR spectrum of bisquaric acid dissolved in DMSO-d_6 showed only three resonances at δ 205.4, 193.6, and 164.6. Both spectra are in full accord with the highly ionized (see pK_a determination, below) and delocalized nature of the system in solution (Figure 1). The significantly lower C=O absorption observed in DMSO solution (1721 cm^{-1}) compared with those seen in KBr (ν_{CO} = 1837 and 1773) is attributed to some resonance delocalization into the end carbonyl groups of the fully ionized form of bisquaric acid (Figure 1). The 1619-cm^{-1} band in the infrared spectrum in DMSO is assumed to be due to the fully delocalized vinylogous carboxylate moiety of the bisquaric acid dianion.

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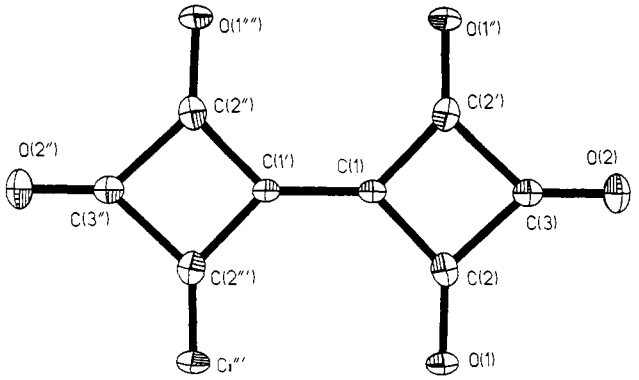

Figure 2. ORTEP diagram depicting 50% thermal ellipsoids and bond distances (Å) and angles (deg) of bisquaric acid: O(2)–C(3) 1.198(7); O(1)–C(2) 1.244(5): C(2)–C(1) 1.428(6); C(2)–C(3) 1.520(6); C(1)–C(1') 1.435(11); O(1)–C(2)–C(1) 135.2(4); O(1)–C(2)–C(3) 134.4(4); C(1)–C(2)–C(3) 90.5(3); C(2')–C(1)–C(2) 93.1(5); C(2')–C(1)–C(1') 133.5(2); C(2)–C(1)–C(1') 133.5(2); O(2)–C(3)–C(2) 137.0(2); O(2)–C(3)–C(2')137.0(2); C(2)–C(3)–C(2') 86.0(4).

The pK_a of bisquaric acid was determined by ultraviolet–visible spectrophotometry.[59] The range of pH needed to determine the pK_a was found by placing **3** in buffers of pH 1, 8, and 12.5 at 25 °C. The UV spectra of **3** at all three pH's were identical, indicating that **3** was totally ionized at pH 1, thus setting an upper limit for study. This process was repeated to determine the limit at which **3** existed totally un-ionized; however, the acidity values fell below the range described by the pH scale necessitating the use of the H_0 scale.[60,61] On analysis, only one pK_a value for **3** was seen and determined to be –4.49 (see Experimental Section). It is presumed that pK_2 was observed and that pK_1 was beyond the range of study. The observation of only three resonances in the ^{13}C NMR spectrum of bisquaric acid in DMSO is in full accord with this assessment. Bisquaric acid is, therefore, significantly more acidic than squaric acid.[62]

In order to understand the solid-state properties of bisquaric acid, small, well-formed crystals were obtained by evaporation of water from a solution of bisquaric acid in 1:1 trifluoromethanesulfonic acid/water. This process produced small, bright yellow, water-free crystals of bisquaric acid, the molecular structure of which is depicted in Figure 2. The asymmetric unit consists of one squaric moiety related by an inversion center to the other. Although the hydrogen atoms were not observed, all oxygen atoms other than those collinear with the axis of the bisquare are involved in hydrogen bonding to equivalent oxygens of adjoining molecules within the same layer. The hydrogen-bonded O(1)···O(1') distances are 2.523 Å. Adjoining layers of bisquaric acid are rotated 90° relative to one another and are separated by 2.674 Å, as depicted in Figure 3. The solid-state structure of squaric acid shows a layered, hydrogen-bonded network where all four oxygen atoms of squaric acid are involved in similar hydrogen bonding within layers (O···O distance 2.572–2.576 Å).[63] The interlayer distance of squaric acid is 2.634 Å.

Properties of Bisquaryls. All symmetrical and unsymmetrical bisquaryls were yellow to orange in color and showed ν_{CO} infrared bands in the region 1786–1730 cm^{-1}, with most bisquaramides showing C=O absorptions at the lower end of the range. Bisquaric acid, **3**, and the parent bisquaramide **4a** were insoluble in many organic solvents; bisquaric acid did not melt, and accurate melting points were not available for **4a** and **4c** due to their decomposition at higher temperatures.

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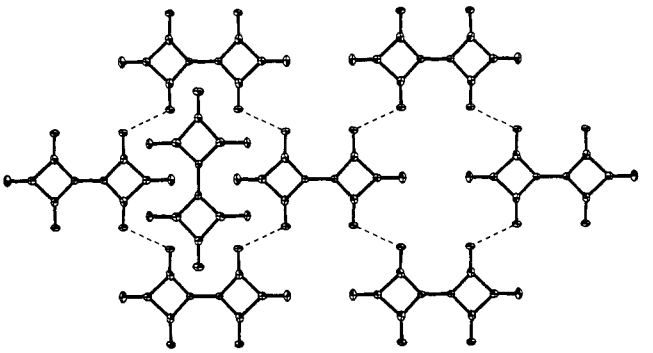

Figure 3. Diagram showing the hydrogen-bonded network of bisquaric acid with only one molecule of the adjoining layer shown.

As seen from the entries in Tables II and III, all isolable 4,4'-bi(cyclobutene-1,2-diones) contain resonance-delocalizing substituents (O, N, Ph). The inability to isolate bisquaryls bearing methyl substituents might be a function of facile enolization of these species, or of an increased susceptibility to nucleophilic addition because of the highly electron deficient nature of the bisquaryl moiety. The related electron deficient acylcyclobutenediones[44] also were not isolable unless a resonance-delocalizing substituent was present. Further studies will be required to establish the full range of preparable bisquaryls.

Conclusions

Palladium–copper cocatalyzed methodologies for the preparation of symmetrical and unsymmetrical 4,4'-bi(cyclobutene-1,2-diones) are described. This new class of unique organic compounds could prove of use in the construction of unusual new materials with interesting properties. Given the very acidic nature of bisquaric acid, it can be anticipated that it will function as a novel, weakly coordinating dianionic ligand for metal complexation. Bisquaric acid and the various bisquaramides should react with salts of metals and metalloids and deliver discrete monomeric as well as polymeric systems. Relevant studies are underway.

Experimental Section

Thin-layer chromatography (TLC) was effected using precoated 0.25-mm silica gel 60F-254 plates from EM Reagents and was visualized by one of the following methods: UV light, phosphomolybdic acid stain, vanillin stain, and anisaldehyde stain. Routine column chromatography was performed using flash grade silica gel 60 (EM Science) with compressed air as the source of positive pressure, unless stated otherwise. Tetrahydrofuran and ether were distilled from sodium and benzophenone under nitrogen or argon. Methylene chloride, acetonitrile, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride. Air sensitive reactions were conducted under an atmosphere of argon or nitrogen in flame- or oven-dried glassware using standard airless techniques.

Starting Materials. Palladium complexes were obtained from commercial sources and used as received: $(PhCH_2)PdCl(PPh_3)_2$ (Aldrich), $Pd_2(dba)_3$ (Aldrich), $Pd(PPh_3)_4$ (Aldrich), $(PPh_3)_2PdCl_2$ (Johnson Matthey). CuI was purified according to the literature method.[64] Triphenylphosphine (Alfa) was recrystallized from ethanol. 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **5**, was prepared by a recently described improved procedure.[44] 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6a**,[7] 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e**,[44] and 3-(1-morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6f**,[44] were prepared by published procedures.

3-(*N*-Methylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, 6b. 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2.269 g, 5.29 mmol) and 1.0 equiv of methylamine (40% aqueous solution) were dissolved in 8 mL of 2-propanol and stirred at room temperature for 40 min. The solvent was removed, and the residue was purified by column chromatography (SiO_2, 1:4 EtOAc/hexanes, R_f = 0.24) to give 1.756 g (83%) of a pale yellow oil (3:1 mixture of rotamers calculated

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by ^{1}H NMR): mp 82–84 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3410, 1768, 1730, 1600; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82 (s, br, 0.75 H, major), 6.60 (s, br, 0.25 H, minor), 3.30 (d, J = 5.1 Hz, 0.75 H, minor), 3.07 (d, J = 5.1 Hz, 2.25 H, major), 1.53–1.11 (m, 18 H), 0.84 (t, J = 7.2 Hz, 9 H). Anal. Calcd for $C_{17}H_{31}NO_2Sn$: C, 51.03; H, 7.81. Found: C, 51.10; H, 7.86.

3-(*N*-*n*-Propylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, 6c. Analogous reaction of 3-(1-methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (3.366 g, 7.84 mmol, 1.0 equiv) with *n*-propylamine (0.464 g, 7.84 mmol, 1.0 equiv) in 10 mL of 2-propanol gave 1.909 g (80%) of an off-white solid (2:1 mixture of rotamers calculated by ^{1}H NMR): mp 52–54 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3398, 3304, 1765, 1728, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (br, s, 0.67 H, major), 5.55 (br, s, 0.33 H, minor), 3.71 (q, J = 6.6 Hz, 0.67 H, minor), 3.30 (q, J = 6.6 Hz, 1.34 H, major), 1.74–0.93 (m, 23 H), 0.89 (t, J = 7.2 Hz, 9 H). Anal. Calcd for $C_{19}H_{35}O_2NSn$: C, 53.30; H, 8.24. Found: C, 53.32; H, 8.26.

3-(*N*-Isopropylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, 6d. Analogous reaction of 3-(methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2.391 g, 5.57 mmol, 1.0 equiv) with isopropylamine (0.329 g, 5.57 mmol, 1.0 equiv) in 8 mL of 2-propanol gave 1.909 g (80%) of **6d** as an off-white solid (2:1 mixture of rotamers calculated by ^{1}H NMR): mp 72–73 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1} 3390, 1768, 1732, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 2.0 Hz, 0.67 H, major), 5.36 (d, J = 2.0 Hz, 0.33 H, minor), 4.47 (m, 0.33 H, minor), 3.68 (m, 0.67 H, major), 1.55–1.48 (m, 6 H), 1.37–1.23 (m, 12 H), 1.19–1.11 (m, 6 H), 0.89 (t, J = 7.2 Hz, 9 H). Anal. Calcd for $C_{19}H_{35}O_2NSn$: C, 53.30; H, 8.24. Found: C, 53.23; H, 8.22.

3-Methyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, 7a. 3-Methyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione-1-ethylene acetal (0.230 g, 0.54 mmol), prepared according to the established procedure,[43] was dissolved in THF (5 mL), and 2 mL of 50% aqueous H_2SO_4 was added. After stirring at room temperature for 3 h, TLC (SiO_2, 30% Et_2O in hexanes) showed the consumption of starting material (starting material R_f = 0.51, product R_f = 0.73). The reaction mixture was partitioned between Et_2O (10 mL) and H_2O (10 mL), the layers were separated, and the water layer was extracted with Et_2O (2 × 10 mL). The combined Et_2O layers were dried (Na_2SO_4), filtered, evaporated, and purified by chromatography (Chromatotron, 1-mm SiO_2, 25% Et_2O in hexanes) to yield 0.160 g (77%) of **7a** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1770, 1760, 1550; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 1.54 (m, 6 H), 1.33 (m, 6 H), 1.21 (m, 6 H), 0.90 (t, J = 7.2 Hz, 9 H). Anal. Calcd for $C_{17}H_{30}O_2Sn$: C, 53.02; H, 7.85. Found: C, 53.27; H, 7.92.

3-Phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,dione, 7b. A suspension of CuCN (0.230 g, 2.54 mmol) in THF (5 mL) was cooled to −78 °C in a flame-dried 100-mL three-necked flask. *n*-Butyllithium (1.8 M in hexane, 3.17 mL, 5.07 mmol) was added in a dropwise manner, and the mixture was stirred at −78 °C for 10 min. The reaction mixture was allowed to warm to 0 °C and stirred until it became homogeneous (approximately 5 min). The solution was recooled to −78 °C and stirred for 20 min. (Trimethylsilyl)tri-*n*-butylstannane[65] (921 mg, 2.54 mmol) was added via syringe, and the mixture was stirred at −78 °C for 20 min, then allowed to warm to room temperature, and stirred for 90 min. The resulting black mixture was recooled to −78 °C, and a solution of 3-(1-methylethoxy)-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal (392 mg in 5 mL THF, 1.69 mmol) was added dropwise, and the mixture was stirred for 1 h at −78 °C. The reaction was quenched at −78 °C by dropwise addition of saturated NH_4Cl solution (10 mL). After warming to room temperature, the mixture was added to H_2O (20 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL) and dried over Na_2SO_4. After filtration and removal of solvent, the residue was chromatographed (gravity column, SiO_2, 1:32 EtOAc/hexanes) to give 464 mg (56%) of 3-phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 1-ethylene acetal as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 2 H), 7.40–7.38 (m, 3 H), 4.23–4.09 (m, 4 H), 1.57–1.49 (m, 6 H), 1.38–1.12 (m, 12 H), 0.86 (t, J = 7.2 Hz, 9 H). HRMS (EI) calcd for $C_{24}H_{36}O_3Sn$: 492.1686. Found: 492.1679.

3-Phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 1-ethylene acetal (5.49 g, 11.2 mmol) was dissolved in 170 mL of THF and cooled to 0 °C, 170 mL of 50% aqueous H_2SO_4 was added, and the reaction mixture was stirred at 0 °C for 2.5 h. TLC analysis showed disappearance of starting material and formation of a new product (SiO_2, 1:4 EtOAc/hexanes, R_f = 0.59 for starting material, R_f = 0.69 for product). The reaction mixture was diluted with 50 mL of Et_2O, and 50 mL of H_2O was added. The water layer was separated and extracted with Et_2O (3 × 40 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (2 × 40 mL), the combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed. The residue was purified by column chromatography (SiO_2, 1:10 EtOAc/hexanes) to give 3.52 g (70%) of **7b** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1770, 1605, 1538; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–7.92 (m, 2 H), 7.59–7.53 (m, 3 H), 1.59–1.49 (m, 6 H), 1.36–1.27 (m, 12 H), 0.87 (t, J = 7.2 Hz, 9 H). HRMS (EI) calcd for $C_{22}H_{32}O_2Sn$: 448.1424. Found: 448.1422.

3-Chloro-4-methyl-3-cyclobutene-1,2-dione, 8a. 3-Hydroxy-4-methyl-3-cyclobutene-1,2-dione[66] (2.045 g, 18.24 mmol) was dissolved in 12 mL of distilled CH_2Cl_2, one drop of DMF was introduced as catalyst, and oxalyl chloride (1.59 mL, 1.0 equiv) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature overnight, producing a bright yellow solution. The solvent was removed by simple distillation, and the residue was distilled under vacuum to give 1.464 g (62%) of a yellow oil: bp 75–80 °C/0.5 mmHg; IR (CH_2Cl_2, cm^{-1}) 1880 (w), 1810 (s), 1777 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s). Spectral data were in agreement with those reported by Bellus (our IR bands were consistently 20 cm^{-1} below literature bands).[56]

3-Bromo-4-methyl-3-cyclobutene-1,2-dione, 8b, was prepared as described for **8a**. A methylene chloride solution (10 mL) of 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione[66] (1.525 g, 13.60 mmol), one drop DMF, and oxalyl bromide (6.80 mL, 1.0 equiv) was stirred under nitrogen at room temperature overnight. Workup and purification by distillation gave 1.739 g (73%) of **8b** as a yellow oil: bp 78–81 °C/0.5 mmHg; IR (CH_2Cl_2, cm^{-1}) 1865, 1810, 1785, 1582; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s). Anal. Calcd for $C_5H_3O_2Br$: C, 34.32; H, 1.73. Found: C, 34.34; H, 1.78.

3-Chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, 8c. Following the procedure of Schmidt,[57] 3,4-dichloro-3-cyclobutene-1,2-dione[67] (4.285 g, 28.39 mmol, 1.0 equiv) was dissolved in 50 mL of distilled CH_2Cl_2 and cooled to 0 °C in an ice bath. 2-Propanol (1.706 g, 28.39 mmol, 1.0 equiv) in 50 mL of CH_2Cl_2 was added dropwise over 10 min, followed by a solution of distilled triethylamine (2.872 g, 28.39 mmol, 1.0 equiv) in 20 mL of CH_2Cl_2. The light yellow solution quickly turned orange in color. The reaction mixture was stirred overnight at room temperature and then refluxed for 30 min. Solvent was removed by simple distillation, 20 mL of distilled E_2O was added to precipitate Et_3N^+H Cl^-, the ether layer was separated by cannulation, and the Et_2O was evaporated, leaving an oil. The crude product was purified by vacuum distillation to give 3.058 g (62%) of a yellow oil: bp 97 °C/0.5 mmHg; IR (CH_2Cl_2, cm^{-1}) 1810, 1770, 1605; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (hept, J = 6.0 Hz, 1 H), 1.51 (d, J = 6.0 Hz, 6 H). Anal. Calcd for $C_7H_7O_3Cl$: C, 48.16; H, 4.04. Found: C, 48.04; H, 4.02.

3-Bromo-4-phenyl-3-cyclobutene-1,2-dione, 8d. 3-Phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7b** (1.245 g, 2.78 mmol, 1.0 equiv), was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C. Bromine (0.445 g, 2.78 mmol, 1.0 equiv) was added dropwise, and the mixture was stirred under argon, producing a bright yellow solution within 45 min. The solvent was removed, and the resulting crude solid was recrystallized from CCl_4 to give 0.615 g (93%) of **8d** as a pale yellow solid: mp 128–129 °C (CCl_4; lit.[68] mp 128–129 °C); IR (CH_2Cl_2, cm^{-1}) 1790, 1600, 1560; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34–8.32 (m, 2 H), 7.73–7.57 (m, 3 H). Anal. Calcd for $C_{10}H_5O_2Br$: C, 50.67; H, 2.13. Found: C, 50.86; H, 2.31.

Bisquaryls by Palladium-Catalyzed Oxidation Homocoupling of Stannylcyclobutene-1,2-diones. 4,4′-Bi(3-amino-3-cyclobutene-1,2-dione), 4a. 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6a** (248 mg, 0.64 mmol), bis(triphenylphosphine)palladium dichloride (9 mg, 2 mol %), and CuI (3 mg, 4 mol %) were dissolved in 5 mL of CH_3CN and stirred at room temperature in a flask equipped with a drying tube charged with calcium sulfate. After 4 h, an orange precipitate was collected on a fine porosity fritted funnel and washed with hexanes (3 × 10 mL) and then with hot THF (3 × 10 mL). The orange solid was dried in vacuo, leaving 53 mg (86%) of **4a**: slow decomposition above 200 °C; IR (KBr pellet, cm^{-1}) 3374, 3266, 1771, 1736, 1626; ^{1}H NMR (300 MHz, DMSO-d_6)

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δ 9.58 (s, br, 2 H), 8.13 (s, br, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.4, 187.6, 180.9, 150.9. HRMS Calcd for $C_8H_4N_2O_4$: 192.0171. Found: 192.0171.

4,4'-Bi(3-(1-piperidinyl)-3-cyclobutene-1,2-dione), 4b. 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e** (170 mg, 0.37 mmol), bis(triphenylphosphine)palladium dichloride (7 mg, 2 mol %), and CuI (3 mg, 4 mol %) were dissolved in 3 mL of CH_3CN and stirred at 50 °C in a flask equipped with a drying tube charged with calcium sulfate. After 3 h, TLC (SiO_2, 20% EtOAc in hexanes) indicated that the reaction was complete. The solvent was evaporated, and the residue was dissolved in 20 mL of CH_3CN and washed with hexanes (3 × 20 mL). The combined acetonitrile layers were evaporated, and the residue was chromatographed (Chromatotron, SiO_2, 2 mm, 40% EtOAc in hexanes), yielding 36 mg (60%) of the bisquaryl **4b** as a yellow solid: mp 232–233 °C (dichloroethane and pentane); IR (CH_2Cl_2, cm^{-1}) 1744, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (m, 4 H), 3.82 (m, 4 H), 1.79 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 185.8, 177.0, 148.1, 50.8, 48.5, 25.6, 25.3, 22.7. Anal. Calcd for $C_{18}H_{20}O_4N_2$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.29; H, 6.16; N, 8.44. HRMS calcd for $C_{18}H_{20}N_2O_4$: 328.1422. Found: 328.1423.

4,4'-Bi(3-(1-morpholinyl)-3-cyclobutene-1,2-dione), 4c. 3-(1-Morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6f** (423 mg, 0.93 mmol), bis(triphenylphosphine)palladium dichloride (14 mg, 2 mol %), and copper(I) iodide (7 mg, 4 mol %) in CH_3CN at room temperature for 3 h showed a new UV active, yellow spot (TLC, SiO_2, 50% ethyl acetate in hexanes, R_f = 0.32). Dilution with 30 mL of acetonitrile, washing with hexanes (3 × 30 mL), and evaporation of the combined CH_3CN layers left an orange-yellow solid that was purified by column chromatography (flash SiO_2, 6 in. × 0.75 in., 50% to 100% ethyl acetate in hexanes) to give 97 mg (67%) of **4c**: mp > 300 °C (acetone and pentane); IR (KBr pellet, cm^{-1}) 1738, 1613; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.92 (m, 4 H), 3.74 (m, 8 H), 3.54 (m, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.0, 186.2, 177.5, 148.3, 66.3, 49.9, 48.0. Anal. Calcd for $C_{16}H_{16}O_6N_2$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.56; H, 4.91; N, 8.33. HRMS calcd for $C_{16}N_2O_6$: 332.100 836. Found 332.100 836.

Unsymmetrical Bisquaryls by Palladium-Catalyzed Cross-Coupling. 3-Amino-3'-(1-methylethoxy)-4,4'-bi(3-cyclobutene-1,2-dione), 9a. An acetonitrile solution (13 mL) of 3-chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.350 g, 2.00 mmol, 1.0 equiv), and 3-amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6a** (0.773 g, 2.00 mmol, 1.0 equiv), was prepared in a 25-mL round-bottomed flask and degassed under nitrogen for 15 min. The solution was treated with a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.076 g, 5 mol %) and CuI (0.019 g, 5 mol %), the solution was stirred for 10 min at room temperature until all solids had dissolved, and the reaction mixture was heated to 50 °C. TLC showed consumption of starting material (SiO_2, 1:1 EtOAc/hexanes, R_f = 0.18) after 4 h. The solvent was removed by rotary evaporator, and the residue was purified by flash silica gel chromatography (1:1 EtOAc/hexanes) to give 0.238 g (50%) of **9a** as an orange solid: mp 165–166 °C with darkening (CH_3CN); IR (CH_3CN, cm^{-1}) 3630, 3540, 3310, 1750, 1650, 1600, 1570; ^{1}H NMR (300 MHz, CD_3CN) δ 7.84 (s, 1 H), 7.60 (s, 1 H), 5.59 (hept, J = 6.0 Hz, 1 H), 1.46 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (75 MHz, CD_3CN) δ 194.5, 193.7, 192.4, 191.0, 186.3, 183.7, 160.7, 148.8, 83.0, 22.6. Anal. Calcd for $C_{11}H_9O_5N$: C, 56.17; H, 3.86. Found: C, 56.18; H, 3.88.

3-(*N*-Methylamino)-3'-(1-methylethoxy)-4,4'-bi(3-cyclobutene-1,2-dione), 9b. An acetonitrile solution (10 mL) of 3-chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.327 g, 1.87 mmol, 1.0 equiv), and 3-(*N*-methylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6b** (0.749 g, 1.87 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.071 g, 5 mol %) and CuI (0.018 g, 5 mol %) were heated to 50 °C for 3 h. Workup and purification by column chromatography (SiO_2, 1:3 EtOAc/hexanes, R_f = 0.20) gave 0.219 g (47%) of **9b** as a yellow solid: mp 155–156.5 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3310, 3270, 1745, 1730, 1640, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 5.67 (hept, J = 6 Hz, 1 H), 3.44 (s, 3 H), 1.50 (d, J = 6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 193.5, 191.3, 188.5, 181.8, 181.5, 159.8, 146.8, 82.6, 32.4, 22.6. Anal. Calcd for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45. Found: C, 57.66; H, 4.44.

3-(1-Methylethoxy)-3'-(*N*-*n*-propylamino)-4,4'-bi(3-cyclobutene-1,2-dione), 9c. An acetonitrile solution (12 mL) of 3-chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.379 g, 2.17 mmol, 1.0 equiv), and 3-(*N*-*n*-propylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6c** (0.929 g, 2.17 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.082 g, 5 mol %) and CuI (0.021 g, 5 mol %) were heated to 50 °C for 4 h. Workup and purification by column chromatography (SiO_2, 1:3 EtOAc/hexanes, R_f = 0.22) gave 0.383 g (64%) of **9c** as a yellow solid: mp 115–117 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3280, 1750, 1635, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1 H), 5.68 (hept, J = 6.0 Hz, 1 H), 3.75 (q, J = 7.0 Hz, 2 H), 1.72 (hext, J = 7.0 Hz, 2 H), 1.53 (d, J = 6.0 Hz, 6 H), 1.01 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 193.5, 191.2, 188.7, 184.0, 181.0, 159.9, 146.6, 82.6, 47.4, 23.8, 22.6, 10.7. Anal. Calcd for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.45. Found: C, 60.37; H, 5.52.

3-(1-Methylethoxy)-3'-(*N*-isopropylamino)-4,4'-bi(3-cyclobutene-1,2-dione), 9d. An acetonitrile solution (10 mL) of 3-chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.321 g, 1.84 mmol, 1.0 equiv), and 3-(*N*-isopropylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6d** (0.788 g, 1.84 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.070 g, 5 mol %) and CuI (0.018 g, 5 mol %) were heated to 50 °C for 3 h. Workup and purification by column chromatography (SiO_2, 1:3 EtOAc/hexanes, R_f = 0.23) gave 0.455 g (91%) of **9d** as an orange solid: mp 138–140 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3350, 1750, 1625, 1610, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 5.68 (hept, J = 6.0 Hz, 1 H), 4.50 (hept, J = 7.0 Hz, 1 H), 1.53 (d, J = 6.0 Hz, 6 H), 1.37 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 193.6, 190.9, 188.5, 183.5, 180.2, 159.9, 146.9, 82.6, 48.7, 23.6, 22.6. Anal. Calcd for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.45. Found: C, 60.47; H, 5.47.

3-(1-Methylethoxy)-3'-(*N*-piperidinyl)-4,4'-bi(3-cyclobutene-1,2-dione), 9e. An acetonitrile solution (10 mL) of 3-chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.317 g, 1.81 mmol, 1.0 equiv), and 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e** (0.824 g, 1.81 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.069 g, 5 mol %) and CuI (0.017 g, 5 mol %) were heated to 50 °C for 4 h. Workup and purification by column chromatography (SiO_2, 1:3 EtOAc/hexanes, R_f = 0.22) gave 0.331 g (60%) of **9e** as a yellow-orange solid: mp 153–154 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 1750, 1630, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (hept, J = 6.0 Hz, 1 H), 4.05 (m, 2 H), 3.70 (m, 2 H), 1.84–1.77 (m, 6 H), 1.53 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 191.4, 190.8, 189.7, 184.7, 175.4, 162.8, 144.7, 81.5, 52.0, 49.3, 26.4, 25.8, 23.2, 22.7. Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65. Found: C, 53.32; H, 5.74.

3-*N*-Isopropylamino-3'-phenyl-4,4'-bi(3-cyclobutene-1,2-dione), 9f, was prepared as described for **9a**. An acetonitrile solution (8 mL) of 3-bromo-4-phenyl-3-cyclobutene-1,2-dione, **8d** (0.340 g, 1.43 mmol, 1.0 equiv), and 3-(*N*-isopropylamino)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6d** (0.614 g, 1.43 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.054 g, 5 mol %) and CuI (0.014 g, 5 mol %) were heated to 50 °C for 2 h. Workup and purification by column chromatography (SiO_2, 1:3 EtOAc/hexanes, R_f = 0.24) gave 0.381 g (90%) of **9f** as a orange solid: mp 182–184 °C (CH_2Cl_2/hexanes); IR (KBr, cm^{-1}) 3494, 3252, 3212, 1786, 1768, 1621, 1573, 1551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (br, s, 1 H), 8.58 (d, J = 7.0 Hz, 2 H), 7.65–7.55 (m, 3 H), 4.61–4.54 (m, 1 H), 1.42 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 191.9, 191.0, 187.0, 184.4, 180.1, 168.6, 147.5, 135.1, 132.3, 129.5, 127.7, 49.0, 23.6. Anal. Calcd for $C_{17}H_{13}O_4N$: C, 69.15; H, 4.44. Found: C, 68.88; H, 4.49.

3-Phenyl-3'-(1-piperidinyl)-4,4'-bi(3-cyclobutene-1,2-dione), 9g, was prepared as described for **9a**. An acetonitrile solution (8 mL) of 3-bromo-4-phenyl-3-cyclobutene-1,2-dione, **8d** (0.357 g, 1.50 mmol, 1.0 equiv) and 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **6e** (0.683 g, 1.50 mmol, 1.0 equiv) and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.057 g, 5 mol %) and CuI (0.014 g, 5 mol %) were heated to 50 °C for 2 h. Workup and purification by column chromatography (SiO_2, 1:2 EtOAc/hexanes, R_f = 0.29) gave 0.251 g (52%) of **9g** as an orange solid: mp 130 °C dec (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 1760, 1630, 1565; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–8.07 (m, 2 H), 7.60–7.52 (m, 3 H), 4.12 (dd, J = 6.0 Hz, J = 4.8 Hz, 2 H), 3.55 (dd, J = 6.0 Hz, J = 4.8 Hz, 2 H), 1.87–1.77 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 194.0, 190.1, 189.2, 184.4, 175.9, 173.4, 145.9, 134.7, 130.9, 129.2, 127.9, 52.3, 49.5, 26.2, 25.7, 23.1. HRMS (EI) calcd for $C_{19}H_{15}O_4N$: 321.1001. Found: 321.1001.

Symmetrical Bisquaryls by Palladium-Catalyzed Cross-Coupling. 4,4'-Bi(3-phenyl-3-cyclobutene-1,2-dione), 4e. An acetonitrile solution (6 mL) of 3-bromo-4-phenyl-3-cyclobutene-1,2-dione, **8d** (0.263 g 1.11 mmol, 1.0 equiv), and 3-phenyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **7b** (0.496 g, 1.11 mmol, 1.0 equiv), and a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.042 g, 5 mol %) and CuI (0.011 g, 5 mol %) were heated to 50 °C for 3 h. The reaction mixture was cooled to room temperature and washed with hexanes (4 × 20 mL), and the hexanes extracts were backwashed with CH_3CN. The combined acetonitrile layers were passed

through a plug of Florisil, and the solvent was removed. The crude product was filtered through a short SiO_2 column with 1:3 EtOAc/hexanes, leaving after evaporation of solvent 0.272 g (78%) of **4e** as a red solid. Further purification was performed by recrystallization from CH_2Cl_2 under an argon atmosphere by slow evaporation: red crystals, mp 150 °C dec; IR (CH_2Cl_2, cm^{-1}) 1770, 1592; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 4 H), 7.68 (t, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 192.4, 190.3, 189.2, 173.9, 135.7, 130.9, 129.7, 126.9. HRMS (EI) calcd for $C_{20}H_{10}O_4$: 314.0579. Found: 314.0579. Solutions of this compound decompose when exposed to air or on prolonged exposure to SiO_2 during chromatography.

4,4'-Bi(3-(1-methylethoxy)-3-cyclobutene-1,2-dione), 4f. 3-Chloro-4-(1-methylethoxy)-3-cyclobutene-1,2-dione, **8c** (0.316 g, 1.81 mmol, 1.0 equiv), and 3-(1-methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione, **5** (0.775 g, 1.81 mmol, 1.0 equiv), were dissolved in 10 mL of distilled CH_3CN, a solid mixture of $(PhCH_2)PdCl(PPh_3)_2$ (0.069 g, 5 mol %) and CuI (0.017 g, 5 mol %) was added, and the reaction mixture was stirred under N_2 at 50 °C for 4 h. The byproduct *n*-Bu_3SnCl was removed from the CH_3CN layer with a wash of hexanes (4 × 15 mL), the CH_3CN was filtered through a short plug of Florisil, and the solvent was removed. The residue was dissolved in 10 mL of CH_2Cl_2, a small amount of activated carbon was added, and the mixture was heated to gentle reflux for 1 h and filtered through a small plug of Celite. The solvent was evaporated, and the crude product was recrystallized from CH_2Cl_2/hexanes to give 0.423 g (84%) of **4f** as a orange solid: mp 124–125 °C (CH_2Cl_2/hexanes); IR (KBr, cm^{-1}) 1760, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (hept, J = 6.0 Hz, 2 H), 1.53 (d, J = 6.0 Hz, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 191.9, 187.5, 159.7, 82.2, 22.8. HRMS (EI) calcd for $C_{14}H_{14}O_6$: 278.0790. Found: 278.0790.

Bisquaric Acid: 4,4'-Bi(3-hydroxy-3-cyclobutene-1,2-dione), 3. Hydrolysis. 4,4'-Bi(3-(1-methylethoxy)-3-cyclobutene-1,2-dione), **4f** (400 mg, 1.73 mmol), was placed in a round-bottomed flask. A minimum amount of THF was added to dissolve the solid, and the resulting orange solid was treated with concentrated HCl (0.2 mL). The reaction mixture was allowed to stir at room temperature open to the air. After 3–4 h, a bright yellow precipitate had formed, and after 6 h, the solid was collected and washed with THF, providing 345 mg (93%) of **3**: did not melt below 270 °C; IR (KBr pellet, cm^{-1}) 3573, 3431 (br), 2428 (br), 1837, 1773, 1196; ^{13}C NMR (75 MHz, DMSO-d_6) δ 205.4, 193.6, 164.6. Anal. Calcd for $C_8H_2O_6 \cdot 0.25\ H_2O$: C, 48.38; H, 1.27. Found: C, 48.41; H, 1.40.

Determination of the pK_a of Bisquaric Acid. Absorbance spectra were obtained with a Varian DMS-200 UV–vis. spectrophotometer. Potassium chloride–hydrochloric acid buffer solution of pH 1, potassium biphthalate buffer of pH 4, and potassium phosphate monobasic–sodium hydroxide buffer solution of pH 8 were obtained from Fisher Scientific and were used as received. A solution of pH 12.5 was prepared from sodium hydroxide and deionized water. Solutions of known H_0[69] were prepared from deionized water and concentrated sulfuric acid obtained from Fisher Scientific. FISHER brand 10-mm rectangular cells for the far UV region were employed. Each cuvette was washed with deionized water and methanol and dried before the next run was performed. Unless otherwise indicated, each run was preceded with a calibration of the reference cuvette and the sample cuvette by zeroing the absorbance reading.

Procedure for Acquiring the Upper and Lower Limits of Study. To determine the upper limit of study, the following procedure was performed. Into each of the two cuvettes was placed 2.90 mL of buffer of pH 1. One cuvette was designed as the reference, and the other, as sample. Into the sample cuvette was placed 50 μL of **3** (1×10^{-3} M solution in H_2O), and the UV spectrum was recorded and plotted. This was repeated for pH 8 and 12.5 to obtain the limit of total ionization. On comparison the UV spectra at all three pH's were found to be identical. To determine the lower H_0 limit and ultimately the pK_a, aqueous solutions of H_2SO_4 ranging from H_0 values of –0.23 (8.30 wt % H_2SO_4) to –11.94 (100 wt % H_2SO_4) were prepared.[59] Following the above procedure for determination of the upper limit, UV spectra of **3** in solutions of 70, 80, and 90 wt % H_2SO_4 were found to be similar enough to set H_0 = –11.94 as the lower limit of study.

Determination of Optimum Wavelength. A series of UV spectra were obtained by placing **3** in different H_2SO_4 solutions (47, 70, 80, and 90 wt %). Overlaying these spectra in a single plot of absorbance (–0.010 to 1.000) versus wavelength (190.0 to 550.0 nm) enabled determination of an optimum wavelength to perform the study and to evaluate the presence of medium effects. Although a true isosbestic point was not observed,[69] a sigmoidal curve was obtained from a plot of H_0 versus absorbance, suggesting a minimal medium effect.[59] In viewing the stacked plots, 377.5 nm was chosen as the wavelength at which the separation of the spectrum of the totally ionized form and the spectrum of the totally unionized form was at a maximum.

(69) Flexser, L. A.; Hammett, L. P.; Dingwall, A. *J. Am. Chem. Soc.* **1935**, *57*, 2103.

Table IV. Log[$(A-A_i)/(A_h-A)$] Values for Determination of pK_a

entry	H_0	absorbance	log[$(A-A_i)/(A_h-A)$]
1	0.09	0.275	
2	–0.23	0.274	
3	–0.42	0.276	
4	–0.64	0.270	
5	–0.90	0.269	
6	–1.21	0.265	
7	–1.41	0.258	
8	–1.69	0.262	
9	–2.03	0.245	0.87
10	–2.22	0.237	0.76
11	–2.45	0.232	0.69
12	–2.69	0.221	0.57
13	–3.13	0.193	0.32
14	–3.60	0.169	0.15
15	–4.51	0.130	–0.12
16	–5.92	0.076	–0.55
17	–7.52	0.048	–0.91
18	–9.03	0.034	–1.23
19	–11.94	0.020	

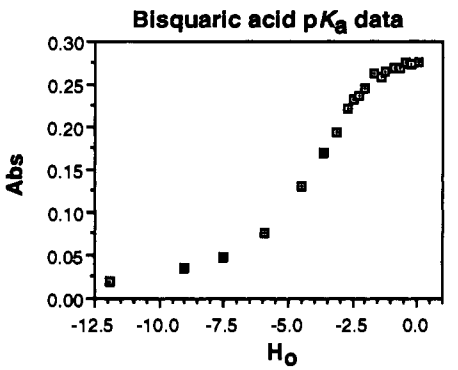

Figure 4. Sigmoidal curve of absorbance versus H_0.

General Procedure for Acquiring Absorbance at Each H_0. Into each of four cuvettes was placed 2.90 mL of a chosen H_2SO_4 solution. One cuvette was designated as the reference, and the other three, as the sample cuvettes. Into the sample cuvette was placed 50 μL of **3** (1×10^{-3} M solution in H_2O), and the absorbance was recorded. This was repeated for the next two sample cuvettes. The absorbance was recorded at 377.5 nm at 20-s intervals for three cycles at 25 °C. Each solution was measured three times, and an average was taken.

From the data in Table IV, a plot of absorbance versus H_0 was obtained to give the sigmoidal curve shown in Figure 4. Each absorbance value was placed into eq 6, where A_i is the absorbance at total ionization (0.02)

$$\log[(A-A_i)/(A_h-A)] \quad (6)$$

and A_h is absorbance at total un-ionization (0.275). Table IV shows the calculated data. The extreme values (entries 1–8 and 19) were omitted since these end values would be overly sensitive to small instrumental errors.[59] A plot of the data in column 4 of Table IV {log[$(A-A_i)/(A_h-A)$] versus H_0 gave a straight line fit with a correlation factor of R^2 = 0.980 and fit the equation $y = 1.3538 + 0.30134x$. In Figure 4, only one pK_a value for **3** was seen, and it was determined to be –4.49 (at y = 0 in Figure 5).

Crystallography. Small yellow crystals of bisquaric acid were grown by slow evaporation of the solution of bisquaric acid in 50% aqueous triflic acid. In contrast to the solid that precipitated on hydrolysis of diisopropyl squarate (see above), this material crystallized without any entrained water. (Anal. Calcd for $C_8H_2O_6$: C, 49.50; H, 1.04. Found: C, 49.43; H, 1.09.) A crystal was mounted on a glass fiber for data collection at ambient temperature on a Siemens P4RA diffractometer equipped with a Cu rotating anode. Cell dimensions were determined from a nonlinear least squares fit of 31 machine-centered reflections (20°

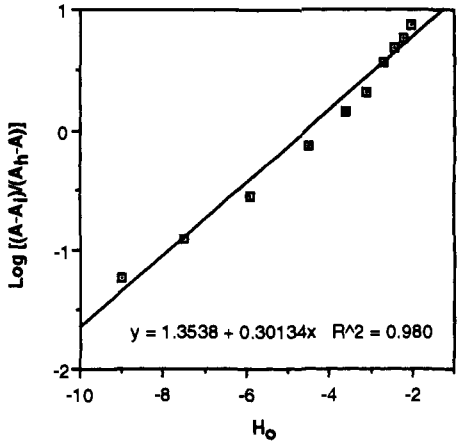

Figure 5. Determination of pK_a: a plot of $\log[(A-A_i)/(A_h-A)]$ versus H_0.

$< 2\theta < 43°$) using the XSCANS data collection program. The Laue symmetry (*4/mmm*) was confirmed by analysis of the intensities of equivalent reflections ($R = 0.027\%$). The structure was solved by direct methods SHELXS-86 and refined with full-matrix least squares on F^2 using all 124 unique data ($2.0° < 2\theta < 114°$) and SHELXL-92 to an equivalent conventional R index of 5.03%. The hydrogen atoms were not located, so none were included in the refinement.

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Supplementary Material Available: Table listing details of the crystallographic data collection, atomic coordinates, bond distances, bond angles, and anisotropic thermal parameters (5 pages); listing of observed and calculated structure factors (2 pages). Ordering information is given on any current masthead page.