Preparation of 3-Acyl-3-cyclobutene-1,2-diones and Some Related Monoacetals

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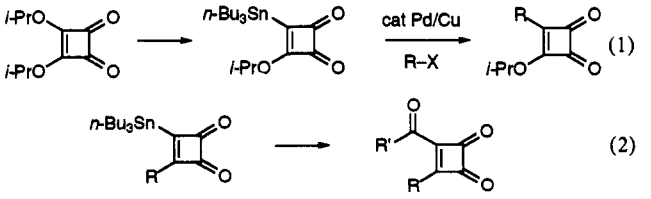
3-(Tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones and 4-methyl-3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-ethylene acetal participate in palladium/copper-cocatalyzed cross-coupling with acyl halides and in palladium-catalyzed carbonylative cross-coupling with aryl/heteroaryl iodides. The derived 3-acyl-3-cyclobutenediones and cyclobutenedione monoacetals should extend the potential of cyclobutenedione-based synthetic organic methodology.

Introduction

The recent development of simple methods for the preparation of substituted cyclobutenediones[1-7] has been crucial to the evolution of new and powerful processes for the synthesis of substituted quinones,[8-20] phenols,[21,22] and substituted alkylidene cyclopentenones.[16,23-27] For example, 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones, prepared from squaric acid esters, are known to undergo modified Stille cross-coupling[28] with vinyl, aryl, and heteroaryl halides and triflates in the presence of cocatalytic palladium and copper to yield substituted cyclobutenediones (eq 1).[4] Of the various classes of substituted cyclobutenediones, those bearing electron-withdrawing functional groups are very scarce.[29-32] As part of a continuing effort to extend the synthetic potential of cyclobutenediones in organic synthesis, the preparation of cyclobutenediones bearing acyl substituents was explored (eq 2). The results of that study are reported herein.



Results and Discussion

Palladium–copper-cocatalyzed cross-coupling of 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones with acid halides was studied as a general entry to 3-acylcyclobutenediones (Table I). The use of cocatalytic palladium and copper was essential for rapid and efficient cross-coupling in this system, as well as in others where transmetalation of an electron-deficient group from tin is desired.[4,12,33-35] Although cross-coupling of 3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1)[4] with various acid halides proceeded well (see below), the anticipated products did not survive attempted purification (SiO_2 chromatography, recrystallization, Kugelrhor distillation). Use of other squarate esters (benzyl, allyl) did not lead to products of improved stability. The instability was due, in part, to very facile hydrolysis of the vinylogous ester, since intentional hydrolysis (1 h, THF/H_2O, catalytic concd HCl) of 3-benzoyl-4-isopropoxy-3-cyclobutene-1,2-dione (**6**, R = Ph) gave the parent acid, 3-benzoyl-4-hydroxy-3-cyclobutene-1,2-dione, (**7a**, R = Ph) as a *stable* bright yellow solid in 69% yield. Unfortunately, an attempt to isolate the free acid of the (2*E*)-butenoyl derivative **6b** was unsuccessful. Nevertheless, the formation of 3-acyl-4-isopropoxy-3-cyclobutene-1,2-diones **6** is general, and this was demonstrated by quenching the cross-coupling reaction mixtures with piperidine, which led to rapid conversion to the stable piperidinyl analogs **8**. Alternatively, a high-yield synthesis of stable amino-substituted acylcyclobutenediones (**8–10**) was achieved by direct cross-coupling of preformed 3-(1-piperidinyl)- (**2**) and 3-(1-

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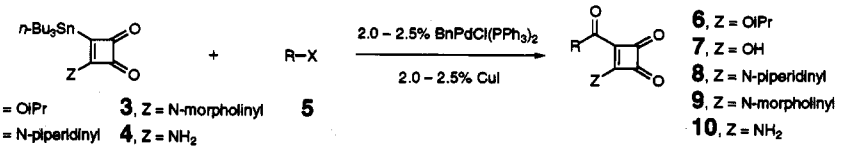
Table I. Palladium/CuI-Catalyzed Cross-Coupling of Stannylcyclobutenediones with Acid Chlorides and Iodobenzene/CO

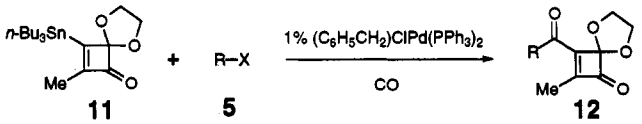


1, Z = OiPr; 2, Z = N-piperidinyl; 3, Z = N-morpholinyl; 4, Z = NH_2; 5

entry	Sn-dione	5	conditions	product	R	yield (%)
1	1	PhCOCl	THF, 50 °C, 15 min	6a	C_6H_5	*a*
2	1	(*E*)-MeCH=CHCOCl	THF, 50 °C, 15 min	6b	(*E*)-propenyl	*a*
3	1	PhCOCl	THF, 50 °C, 20 min then H_3O^+	7a	C_6H_5	69
4	1	PhCOCl	THF, 50 °C, 90 min then $C_5H_{11}N$	8a	C_6H_5	79
5	1	(*E*)-MeCH=CHCOCl	THF, 50 °C, 30 min then $C_5H_{11}N$	8b	(*E*)-propenyl	68
6	1	*p*-$MeOC_6H_4COCl$	THF, 50 °C, 30 min then $C_5H_{11}N$	8c	*p*-$(MeO)C_6H_4$	65
7	2	PhCOCl	THF, 50 °C, 15 min	8a	C_6H_5	92
8	2	(*E*)-MeCH=CHCOCl	THF, 50 °C, 30 min	8b	(*E*)-propenyl	83
9	2	*p*-$(MeO)C_6H_4COCl$	THF, 50 °C, 45 min	8c	*p*-$(MeO)C_6H_4$	67
10	2	CH_2=CHCOCl	THF, 50 °C, 60 min	8d	ethenyl	64
11	2	*o*-$(OAc)C_6H_4COCl$	BHT,[b] THF, 25 °C, 180 min	8e	*o*-$(OAc)C_6H_4$	88
12	2	$EtOCOCH_2COCl$	THF, 50 °C, 30 min	8f	$EtOCOCH_2$	41
13	2	*o*-$(OMEM)C_6H_4COCl$	BHT,[b] THF, 25 °C, 180 min	8g	*o*-$(OMEM)C_6H_4$	70
14	3	PhCOCl	THF, 50 °C, 60 min	9a	C_6H_5	73
15	3	*o*-$(OAc)C_6H_4COCl$	THF, 25 °C, 120 min	9b	*o*-$(OAc)C_6H_4$	73
16	4	PhCOCl	THF, 50 °C, 20 min	10a	C_6H_5	84
17	4	(*E*)-MeCH=CHCOCl	THF, 50 °C, 15 min	10b	(*E*)-propenyl	93
18	4	*p*-$(MeO)C_6H_4COCl$	THF, 50 °C, 20 min	10c	*p*-$(MeO)C_6H_4$	98
19	4	CH_2=CHCOCl	THF, 50 °C, 15 min	10d	ethenyl	53
20	4	*o*-$(OAc)C_6H_4COCl$	BHT,[b] THF, 25 °C, 120 min	10e	*o*-$(OAc)C_6H_4$	65
21	2	PhI	THF, 50 °C, 1 atm CO, 40 h	8a	C_6H_5	65

[a] These compounds were unstable to attempted purification. [b] BHT: 2,6-di-*tert*-butyl-4-methylphenol added to minimize byproduct formation. See text.

Table II. Palladium/CuI-Catalyzed Cross-Coupling of Stannylcyclobutenedione Monoacetals with Acid Chlorides and Aromatic and Heteroaromatic Iodides



entry	5	conditions	product	R	yield (%)
1	PhCOCl	benzene, 80 °C, 1 atm CO	12a	C_6H_5	78
2	*p*-$(MeO)C_6H_4COCl$	benzene, 80 °C, 1 atm CO	12b	*p*-$(MeO)C_6H_4$	92
3	MeCOCl	benzene, 80 °C, 1 atm CO	12c	Me	68
4	*i*-PrCOCl	benzene, 80 °C, 1 atm CO	12d	*i*-Pr	64
5	PhI	benzene, 80 °C, 32 psi CO	12a	C_6H_5	86
6	*p*-$(MeO)C_6H_4I$	benzene, 80 °C, 32 psi CO	12b	*p*-$(MeO)C_6H_4$	81
7	2-Iodothiophene	benzene, 80 °C, 32 psi CO	12e	2-thienyl	53

morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (3) as well as the parent amide, 3-amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (4). Carbonylative cross-coupling of stannylcyclobutenedione (2) with iodobenzene also proved feasible, suggesting an alternative entry to a variety of acylcyclobutenediones. In a number of slower reactions, the formation of a bicyclobutenedione side-product by homocoupling of the (tri-*n*-butylstannyl)-cyclobutenedione was noted,[36] and in these cases catalytic 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture in an effort to minimize byproduct formation.[37]

An attempt to form an acylcyclobutenedione, where Z ≠ a heteroatom substituent (Table I), by palladium-catalyzed cross-coupling of 3-methyl-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (prepared by hydrolysis of the corresponding monoketal[4]) with PhCOCl was unsuccessful. The sensitivity of acylcyclobutenediones not bearing an electron-donating amino substituent is probably due to a strong tendency to hydrate one of the carbonyl groups or to add nucleophiles in a conjugate addition fashion to the cyclobutenedione double bond,[31] a consequence of the vinylogous 1,2,3-triketone nature of the system. Temporary protection of one of the cyclobutenedione carbonyl groups should diminish this reactivity.

To test this hypothesis in a limited way, 4-methyl-3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-ethylene acetal (11) was prepared following literature precedent.[5] Listed in Table II are the results of reaction of 11 with acid halides in benzene at 80 °C in the presence of 1 mol% $(PhCH_2)ClPd(PPh_3)_2$ and 1 atm CO (to suppress formation of the decarbonylation product) producing good yields of 3-acyl-4-methyl-3-cyclobutene-1,2-dione 2-(ethylene acetal)s 12. Carbonylative cross-coupling of 11 with two iodo aromatics and with iodothiophene at 32 psi CO proceeded well providing an alternative entry to acylcyclobutenedione monoacetals 12. Although initial attempts to provide the free acylcyclobutenedione by hydrolysis of the acetal were unsuccessful, the derived monoacetals could serve as useful functional equivalents of acylcyclobutenediones in a

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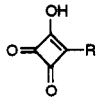
(37) The use of catalytic BHT to minimize organostannane homocoupling was suggested in a personal communication by V. Farina of Bristol-Myers Squibb Pharmaceutical Research Institute.

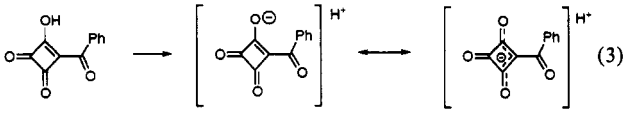
Table III. pK_a Values of Some Semisquaric Acids[39] and Two Relevant Phenols



R	pK_a
H	0.0 ± 0.005
Me	0.20 ± 0.01
t-Bu	0.28 ± 0.05
Ph	−0.22 ± 0.1
4-ClC_6H_4	−0.32 ± 0.1
ClF_2CCH_2	−1.12 ± 0.1
	10.28 (aqueous)[40]
	11.36 (50% aqueous dioxane)[41]

variety of processes where the protected ketone is liberated after the cyclobutenedione has been transformed.

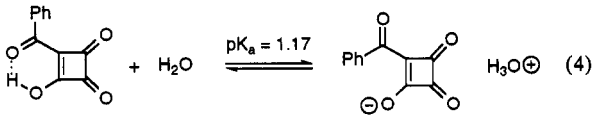
Once in pure form all pertinent physical data for **7a** was obtained including ^{13}C NMR, combustion analysis, and pK_a. The ^{13}C NMR spectrum showed only four different carbon resonances aside from the phenyl ring, a result expected from the resonance equivalency of the two carbons at the ends of the vinylogous acid (eq 3). This is



(3)

a phenomenon observed for a variety of hydroxycyclobutenediones whose ^{13}C NMR spectra have been recorded.

The pK_a of 3-benzoyl-4-hydroxy-3-cyclobutene-1,2-dione, **7a**, was determined to be 1.17 in water (eq 4).[38]



(4)

This value is significantly higher than that anticipated based on the pK_a's of other hydroxycyclobutenediones (Table III).[39] The higher than expected pK_a might be explained by significant H-bonding stabilization of the conjugate acid, a factor unavailable to the hydroxycyclobutenediones listed in Table III. Alternatively, the higher pK_a might be due to diminished solvation, and hence diminished stabilization, of the conjugate base. A similar trend in pK_a's comparing *o*-cresol and 2-hydroxybenzophenone is also noted.

Conclusions

4-Heteroalkyl-3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones and 4-methyl-3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-ethylene acetal participate in palladium/copper-cocatalyzed cross-coupling with acyl halides and in palladium-catalyzed carbonylative cross-coupling with aryl/heteroaryl iodides. The derived highly functionalized cyclobutenediones represent interesting new scaffolds for the construction of useful organic systems.

Experimental Section

Materials and Methods. Thin-layer chromatography (TLC) was effected using precoated 0.25-mm silica gel 60F-254 plates from EM Reagents and were visualized by one or more of the following methods: UV light, phosphomolybdic acid stain, vanillin stain, and anisaldehyde stain. Flash column chromatography was conducted using flash grade silica gel obtained from various vendors. Radial chromatography was performed on a Model 7924 Chromatotron from Harrison Research. Rotors were coated with silica gel PF-254 type 60 with $CaSO_4 \cdot {}^1/_2H_2O$ binder. Combustion analyses were performed by Atlantic Microlabs of Norcross, GA.

Solvents were dried prior to use. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium and benzophenone under nitrogen or argon. Methylene chloride, acetonitrile, triethylamine, and trimethylsilyl chloride were distilled from CaH_2. CuI was purified according to literature procedures.[42,43] Other reagents were used as obtained unless otherwise specified. 3,4-Bis(1-methylethoxy)-3-cyclobutene-1,2-dione was prepared according to a literature procedure.[7] Air-sensitive reactions were conducted under an atmosphere of argon or nitrogen in flame or oven-dried glassware using standard inert atmosphere techniques.

Preparation of Stannylcyclobutenediones 1–4. 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1): An Improved Procedure. 3,4-Bis(1-methylethoxy)-3-cyclobutene-1,2-dione[7] (6.73 g, 34.0 mmol) and (tri-*n*-butylstannyl)trimethylsilane[44] (12.6 g, 34.6 mmol) in dry THF (150 mL) cooled to −23 °C were treated with catalytic tetra-*n*-butylammonium cyanide (186 mg, 2 mol%, Fluka) with monitoring by TLC (SiO_2, 20% ethyl acetate in hexanes). After 3 h, the completed reaction was quenched at −23 °C with 40 mL of saturated aqueous NH_4Cl, and the reaction mixture was diluted with 200 mL of Et_2O and washed with H_2O (2 × 100 mL) and then with brine (100 mL). After drying the organic phase over Na_2SO_4, column chromatography (flash SiO_2, 10 × 2 in., 5% ethyl acetate in hexanes) gave 12.55 g (86%) of 3-(1-methylethoxy)-4-(tri-n-butylstannyl)-3-cyclobutene-1,2-dione (1) with spectral data identical to that described earlier.[4]

3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (2.11 g, 4.91 mmol) was dissolved in CH_2Cl_2 (30 mL) and piperidine (0.73 mL, 7.40 mmol) was added. The reaction was monitored by TLC (SiO_2, 20% ethyl acetate in hexanes) which revealed the formation of a single UV active spot (R_f = 0.57). After 30 min, evaporation of solvent and chromatography (flash SiO_2, 30% ethyl acetate in hexanes, 6 × 1 in.) gave 2.10 g (94%) of 3-(1-piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1765, 1720, 1590; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (br s, 2H), 3.38 (br s, 2H), 1.73 (br s, 6H), 1.58–1.47 (m, 6H), 1.40–1.24 (m, 6H), 1.22–1.12 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 9H). Anal. Calcd for $C_{21}H_{37}NO_2Sn$: C, 55.53; H, 8.21. Found: C, 55.52; H, 8.30.

3-(4-Morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (3). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (2.42 g, 5.64 mmol), and morpholine (1.40 mL, 16.92 mmol) were stirred at room temperature in 40 mL of CH_2Cl_2. The reaction was monitored by TLC (SiO_2, 20% ethyl acetate in hexanes). After 5 h, removal of solvent and chromatography (Chromatotron, SiO_2, 20% ethyl acetate in hexanes) gave 1.96 g (76%) of **3** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1783, 1748, 1646, 1635, 1594; ^1H NMR (300 MHz, $CDCl_3$): δ 4.02 (t, *J* = 4.7 Hz, 2 H), 3.78 (m, 4 H), 3.41 (t, *J* = 4.7 Hz, 2 H), 1.56–1.43

(38) We thank D. Butcher of Bristol-Myers Squibb Pharmaceutical Research and Development for determining this value and Dr. Richard Partyka for arranging the assay.

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(m, 6 H), 1.37–1.23 (m, 6 H), 1.18–1.15 (m, 6 H), 0.87 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.8, 191.8, 189.3, 174.4, 66.8, 65.9, 49.1, 40.0, 28.9, 27.0, 13.5, 10.8. Anal. Calcd for $C_{20}H_{35}O_3NSn$: C, 52.66; H, 7.73; N, 3.07. Found: C, 52.57; H, 7.75; N, 3.02.

3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (4). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (2.11 g, 4.91 mmol) was dissolved in 40 mL of CH_2Cl_2 and cooled to 0 °C. Ammonia was bubbled into the stirred solution and the reaction was monitored by TLC (SiO_2, 20% ethyl acetate in hexanes). After 45 min, the starting material had been consumed and TLC indicated the presence of one new UV visible spot (R_f = 0.27). Removal of solvent and column chromatography (flash SiO_2, 6 × 1 in., 40% ethyl acetate in hexanes) gave 1.86 g (98%) of 4 as an off-white solid with spectral data identical to that described earlier.[10]

Other Starting Materials. Methyl Salicylate MEM Ether.[45] Methyl salicylate (3.64 g, 23.5 mmol) was dissolved in CH_2Cl_2 (50 mL). MEM chloride (4.02 mL, 35.0 mmol) and diisopropylethylamine (6.14 mL, 35 mmol) were added. The reaction was allowed to stir at room temperature and was monitored by TLC (SiO_2, 10% ethyl acetate in hexanes). After 40 h the reaction was diluted with 150 mL of Et_2O and washed with water (3 × 150 mL) and brine (150 mL) and dried over Na_2SO_4. Chromatography (flash SiO_2, 10 × 2 in., 30% ethyl acetate in hexanes) gave 4.75 g (83%) of a clear colorless oil: IR (CH_2Cl_2, cm^{-1}) 1721; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 1.7, 7.8 Hz, 1 H), 7.43 (dt, J = 1.7, 7.8 Hz, 1 H), 7.23 (d, J = 8.4 Hz, 1 H), 7.04 (t, J = 8.4 Hz, 1 H), 5.33 (s, 2 H), 3.80 (s, 3 H), 3.78 (t, J = 4.7 Hz, 2 H), 3.47 (t, J = 4.7 Hz, 2 H), 3.29 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4, 156.4, 133.1, 131.4, 121.4, 121.2, 116.2, 93.8, 71.3, 67.8, 58.7, 51.8. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.10; H, 6.72.

Salicylic Acid MEM Ether. Methyl salicylate MEM ether (1.19 g, 4.91 mmol) was dissolved in 45 mL of anhydrous Et_2O, and potassium trimethylsilanoate (756 mg, 5.89 mmol) was added. The reaction was monitored for the consumption of starting material by TLC (SiO_2, 30% ethyl acetate in hexanes). After 24 h the reaction was filtered and the precipitate washed with Et_2O (3 × 30 mL). The white solid was dissolved in distilled water, and the solution was acidified to pH = 4 by addition of 1.0 N HCl and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and solvent was removed in vacuo to leave 1.01g (91%) of a white solid: mp 57 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 3309 (br), 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, br, 1 H), 8.05 (dd, J = 1.7, 7.8 Hz, 1 H), 7.47 (dt, J = 1.7, 7.8 Hz, 1 H), 7.25 (d, J = 7.5 Hz, 1 H), 7.08 (t, J = 7.5 Hz, 1 H), 5.44 (s, 2 H), 3.86 (m, 2 H), 3.52 (m, 2 H), 3.31 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.6, 156.2, 134.6, 133.0, 122.5, 118.6, 115.1, 94.4, 71.4, 68.8, 58.8. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.51; H, 6.27.

2-Acetyoxybenzoyl Chloride. Acetylsalicylic acid (4.73 g, 26.2 mmol) was suspended in anhydrous benzene (70 mL) and cooled to 0 °C. Oxalyl chloride (4.58 mL, 52.4 mmol) was added followed by three drops of DMF. Gas evolution was observed and the reaction was allowed to warm to room temperature over 1 h. After 6 h, the carboxylic acid had dissolved and the gas evolution had ceased. The solvent and excess $(COCl)_2$ were removed in vacuo. The product, 4.42 g (85%), was isolated by bulb-to-bulb distillation (80 °C at 250 mmHg) as an off-white solid with physical data identical to those reported in the literature.[46]

Palladium–Copper-Cocatalyzed Acylations of 1. Attempted Direct Isolation of 6. 3-Benzoyl-4-(1-methylethoxy)-3-cyclobutene-1,2-dione (6a). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (132 mg, 0.31 mmol), benzoyl chloride (36 μL, 0.31 mmol), benzylchlorobis(triphenylphosphine)palladium (4.5 mg, 2.5 mol%), and CuI (1.5 mg, 2.5 mol%) were stirred at 50 °C in 2 mL of THF. After 15 min, consumption of starting material was indicated by TLC (SiO_2, 20% ethyl acetate in hexanes). The reaction mixture was cooled to rt, solvent was evaporated, and the green residue was dissolved in CH_3CN (30 mL) and washed with hexanes (3 × 20 mL). The acetonitrile phase was removed in vacuo leaving 63 mg (84%) of a green oil: IR (KCl cells, CH_2Cl_2, cm^{-1}) 1795, 1784, 1651; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.12–8.04 (m, 2 H), 7.72–7.63 (m, 1 H), 7.58–7.50 (m, 2H), 5.53 (heptet, J = 6.2 Hz, 1 H), 1.50 (d, J = 6.2 Hz, 6 H). This material could not be purified.

3-((*E*)-2-Butenoyl)-4-(1-methylethoxy)-3-cyclobutene-1,2-dione (6b). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (137 mg, 0.32 mmol), (*E*)-2-butenoyl chloride (30.5 μL, 0.32 mmol), benzylchlorobis(triphenylphosphine)palladium (6.0 mg, 2.5 mol%), and CuI (1.5 mg, 2.5 mol%) were stirred in THF at 50 °C. Monitoring by TLC (SiO_2, 10% ethyl acetate in hexanes) indicated complete reaction after 15 min. The reaction was allowed to cool and acetonitrile (20 mL) was added. After washing with hexanes (3 × 30 mL), the solvent was removed in vacuo leaving a dark green oil: IR (KCl cells, CH_2Cl_2, cm^{-1}) 1782, 1662, 1642, 1614; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dq, J = 20.5, 7.0 Hz, 1 H), 6.68 (dd, J = 1.3 Hz, J = 15.6 Hz, 1 H), 5.56 (heptet, J = 6.3 Hz, 1 H), 2.01 (dd, J = 1.3 Hz, J = 7.0 Hz, 3 H), 1.50 (d, J = 6.1 Hz, 6 H). This material could not be purified.

Hydrolysis of 6a to 7a. 3-Benzoyl-4-hydroxy-3-cyclobutene-1,2-dione (7a). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (729 mg, 1.70 mmol), benzoyl chloride (0.20 mL, 1.70 mmol), and a 1:1 mole ratio of benzylchlorobis(triphenylphosphine)palladium (32 mg, 2.5 mol%) and CuI (8.1 mg, 2.5 mol%) were dissolved in 3 mL of THF and stirred at 50 °C. Monitoring by TLC (SiO_2, 20% ethyl acetate in hexanes) indicated complete reaction after 20 min. The reaction was allowed to cool and the solvent was removed in vacuo leaving a dark brown residue that was taken up in CH_3CN (15 mL) and washed with hexanes (3 × 10 mL). The acetonitrile layer was concentrated and the green residue was stirred for 1 h in 5 mL THF/1.5 mL H_2O and 5 drops of concd HCl. The reaction mixture was diluted with 30 mL of H_2O and washed with Et_2O (3 × 20 mL). The aqueous layer was concentrated and dried in vacuo leaving an orange solid that was sublimed (85 °C at 10^{-5} mmHg) giving 238 mg (69%) of a bright yellow solid: mp 154–156 °C dec; IR (KBr pellet, cm^{-1}) 3420 (br), 1783, 1748, 1646, 1635; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.51 (s, br, 1 H), 8.02 (m, 2 H), 7.56–7.41 (m, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 221.7, 193.4, 185.0, 173.0, 137.2, 132.5, 128.7, 128.1. Anal. Calcd for $C_{11}H_6O_4$: C, 65.34; H, 2.99. Found: C, 65.14; H, 3.06.

Determination of pK_a of 7a.[38] The titration was performed with a Brinkman 665 Dosimat controlled by the Brinkman 670 Titroprocessor. Approximately 0.3 mmol of **7a** was dissolved in 25 mL of a 60% MeOH/40% water mixture. The titrant was 0.0986 M NaOH in water (Aldrich volumetric standard), and the pH of the solution was monitored by a Brinkman combined pH glass electrode. The resulting pK_a was compared to a set of standards run in the same solvent mixture and whose pK_a's were known. From this plot, the aqueous pK_a of **7a** was calculated according to pK_a(org) = pK_a(aq) + 1.214.

In Situ Trapping with Piperidine To Give 8. 3-Benzoyl-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8a). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (99 mg, 0.23 mmol), benzoyl chloride (0.027 mL, 0.23 mmol), benzylchlorobis(triphenylphosphine)palladium (4.4 mg, 2.5 mol%), and CuI (1.1 mg, 2.5 mol%) were dissolved in 1.5 mL of THF and heated to 50 °C. After 90 min, TLC monitoring (SiO_2, 25% ethyl acetate in hexanes) indicated disappearance of 1, and piperidine (0.023 mL, 0.23 mmol) was added. After 1 h at room temperature, solvent was removed and the residue was dissolved in 15 mL of acetonitrile and extracted with hexanes (3 × 15 mL). The combined hexane layers were extracted again with 10 mL of acetonitrile. The combined acetonitrile layers were concentrated by rotary evaporation and the product was isolated by chromatography (Chromatotron, SiO_2, 2 mm, 30% ethyl acetate in hexanes) giving 48 mg (79%) of a yellow solid: mp 136 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 1778, 1755, 1639, 1618; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–7.96 (m, 2 H), 7.70–7.55 (m, 1 H), 7.55–7.45 (m, 2 H), 4.09 (m, 2 H), 3.80 (m, 2 H), 1.80 (m, 6 H); ^{13}C NMR: (75.5 MHz, $CDCl_3$): δ 195.6, 186.3, 183.8, 177.6, 156.5, 135.9, 133.6, 129.3, 128.0, 51.8, 49.2, 25.9, 25.2,

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22.7. Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61. Found: C, 71.29; H, 5.61.

3-((*E*)-2-Butenoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8b). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (137 mg, 0.32 mmol) and crotonyl chloride (0.031 mL, 0.32 mmol) were dissolved in 1.5 mL of dry THF. Benzylchlorobis(triphenylphosphine)palladium (6.0 mg, 2.5 mol%) and CuI (1.5 mg, 2.5 mol %) were added, and the reaction was heated to 50 °C. After 30 min, TLC (SiO_2, 10% ethyl acetate in hexanes) indicated consumption of starting material. The reaction was cooled to room temperature, and piperidine (0.032 mL, 0.32 mmol) was added. After an additional 30 min, the reaction was processed in an identical manner to that for 8a above, yielding 49 mg (68%) of 8b as a yellow solid: mp 110 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 1772, 1754, 1655, 1626; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (A of AB quartet, J = 15.4 Hz, 1H), 7.08 (B of AB quartet, J = 15.4, 5.7 Hz, 1H), 4.14 (m, 2 H), 4.05 (m, 2 H), 1.97 (d, J = 5.5 Hz, 3 H), 1.78–1.68 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.6, 185.9, 181.9, 176.3, 155.3, 145.6, 129.5, 53.3, 49.2, 26.1, 25.6, 22.8, 18.0. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.92; H, 6.49; N, 6.01. Found: C, 66.85; H, 6.50; N, 5.97.

3-(4-Methoxybenzoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8c). 3-(1-Methylethoxy)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (1) (209 mg, 0.48 mmol) and *p*-anisoyl chloride (83 mg, 0.48 mmol) were dissolved in 2 mL of dry THF. Benzylchlorobis(triphenylphosphine)palladium (9.1 mg, 2.5 mol%) and CuI (2.3 mg, 2.5 mol %) were added, and the reaction mixture was heated to 50 °C. After 30 min, TLC (SiO_2, 10% ethyl acetate in hexanes) indicated consumption of starting material. The reaction mixture was cooled to room temperature, piperidine (0.048 mL, 0.48 mmol) was added, and after 30 min the reaction was processed in an identical manner to that for 8a above, yielding 94 mg (65%) of 8c as a yellow solid: mp 134 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 1780, 1756, 1637, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 4.07 (m, 2 H), 3.87 (s, 3 H), 3.75 (m, 2 H), 1.90–1.68 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.4, 184.5, 184.0, 177.7, 164.0, 157.5, 131.8, 129.0, 113.4, 55.0, 51.5, 49.1, 25.9, 25.2, 22.7. Anal. Calcd for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.73; N, 4.68. Found: C, 68.05; H, 5.76; N, 4.72.

Palladium-Catalyzed Acylations of 2. 3-Benzoyl-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8a). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (50 mg, 0.11 mmol) and benzoyl chloride (0.012 mL, 0.11 mmol) were dissolved in 1.5 mL of dry THF in an oven-dried flask. Benzylchlorobis(triphenylphosphine)palladium (2.1 mg, 2.5 mol%) and CuI (0.5 mg, 2.5 mol %) were added, and the reaction was heated to 50 °C. Monitoring by TLC (SiO_2, 30% ethyl acetate in hexanes) indicated consumption of starting material and appearance of a new yellow spot (R_f = 0.52, UV visualization). The reaction mixture was cooled, solvent was evaporated, and the residue was dissolved in 15 mL of acetonitrile and washed with hexanes (3 × 15 mL). The combined hexane layers were back-extracted with 10 mL of acetonitrile, and the combined acetonitrile solutions were concentrated by rotary evaporation, and the product was isolated by chromatography (Chromatotron, SiO_2, 2 mm, 30% ethyl acetate in hexanes) as a yellow solid in 92%, 26.7 mg. Physical data listed above.

3-((*E*)-2-Butenoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8b). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (132 mg, 0.29 mmol) and crotonyl chloride (0.028 mL, 0.29 mmol) were dissolved in 1.5 mL of dry THF in an oven-dried flask. Benzylchlorobis(triphenylphosphine)palladium (5.5 mg, 2.5 mol%) and CuI (1.4 mg, 2.5 mol%) were added, and the reaction mixture was heated to 50 °C for 30 min; TLC monitoring (SiO_2, 20% ethyl acetate in hexanes) showed complete disappearance of starting material after 30 min and appearance of a new yellow spot (R_f = 0.29, UV visualization). Processing of the reaction mixture as for 8a (this section above) and chromatography (flash SiO_2, 10 × 3/4 in., 0% then 30% ethyl acetate in hexanes) gave 56 mg (83%) of product as a yellow-orange solid. Physical data listed above.

3-(4-Methoxybenzoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8c). 3-(1-Piperidinyl)-4-(tri-n-butylstannyl)-3-cyclobutene-1,2-dione (2) (98 mg, 0.215 mmol), anisoyl chloride (37 mg, 0.215 mmol), benzylchlorobis(triphenylphosphine)palladium (4.0 mg, 2.5 mol%), and CuI (1.0 mg, 2.5 mol%) were dissolved in THF and heated to 50 °C for 45 min; TLC monitoring (SiO_2, 30% ethyl acetate in hexanes) showed complete reaction after 45 min and appearance of a new yellow spot (R_f = 0.28, UV visualization). Workup as above for 8a (this section above) and chromatography (Chromatotron, SiO_2, 2 mm, 25% ethyl acetate in hexanes) gave 43 mg (67%) of 8c a bright yellow solid. Physical data listed above.

3-Acrylyl-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8d). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (107 mg, 0.235 mmol), acrylyl chloride (0.019 mL, 0.235 mmol), benzylchlorobis(triphenylphosphine)palladium (4.5 mg, 2.5 mol%), and CuI (1.1 mg, 2.5 mol%) were dissolved in 1.5 mL of THF and heated to 50 °C for 1 h; TLC monitoring (SiO_2, 30% ethyl acetate in hexanes) showed product at R_f = 0.44 (UV visualization). The reaction was cooled, solvent was evaporated, and the brownish-orange residue was dissolved in 20 mL of acetonitrile and washed with hexanes (3 × 20 mL). The combined hexane layers were extracted once with 10 mL of acetonitrile. The combined acetonitrile layers were concentrated and chromatographed (Chromatotron, SiO_2, 2 mm, 25% ethyl acetate in hexanes) to give 33 mg (64%) of 8d as a yellow-orange solid: mp 82–83 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 1775, 1757, 1655, 1621; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, J = 6.9, 10.4 Hz, 1 H), 6.44 (dd, J = 1.6, 6.9 Hz, 1 H), 5.87 (dd, J = 1.6, 10.4 Hz, 1 H), 4.18 (m, 2 H), 4.07 (m, 2 H), 1.86–1.68 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.5, 185.8, 182.0, 176.1, 154.4, 133.9, 129.8, 53.5, 49.3, 26.2, 25.7, 22.8. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.98; N, 6.30. Found: C, 65.66; H, 6.02; N, 6.30.

3-(2-Acetoxybenzoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8e). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (3.53 g, 7.77 mmol) and 2-acetoxybenzoyl chloride (1.52 g, 7.77 mmol) were dissolved in 50 mL of THF. Benzylchlorobis(triphenylphosphine)palladium (117 mg, 2 mol%), copper iodide (29 mg, 2 mol%) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (34 mg, 2 mol%) were added, and the reaction mixture was stirred at room temperature for 3 h. TLC monitoring (SiO_2, 30% ethyl acetate in hexanes) showed disappearance of starting material and the presence of two new yellow spots at this time. One of the spots (R_f = 0.17) was the desired product, 8e, while the other (R_f = 0.04) was a dimer derived from the stannylcyclobutenedione 2. The reaction mixture was then diluted with CH_3CN (100 mL) and washed with hexanes (3 × 80 mL). The acetonitrile layer was concentrated and 2.25 g (88%) of the orange product was isolated by chromatography (flash SiO_2, 8 × 2 in., gradient 30–50% ethyl acetate in hexanes): mp 182–183 °C; IR (CH_2Cl_2, cm^{-1}) 1779, 1757, 1642, 1615; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84–7.76 (m, 1 H), 7.65–7.55 (m, 1 H), 7.43–7.34 (m, 1 H), 7.22–7.13 (m, 1 H), 4.07 (m, 2 H), 3.82 (m, 2 H), 2.27 (s, 3 H), 1.76 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.1, 184.9, 184.4, 176.5, 169.3, 154.2, 148.9, 134.3, 131.5, 130.6, 126.2, 123.7, 52.3, 49.5, 26.2, 25.7, 23.0, 21.0. Anal. Calcd for $C_{18}H_{17}O_5N$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.96; H, 5.22; N, 4.29.

3-(1-Oxo-2-carbethoxyethyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8f). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (100 mg, 0.22 mmol), ethyl malonyl chloride (0.028 mL, 0.22 mmol), benzylchlorobis(triphenylphosphine)palladium (4.2 mg, 2.5 mol%), and CuI (1.0 mg, 2.5 mol%) were dissolved in 2 mL of dry THF and heated to 50 °C in an oven-dried flask for 30 min until TLC monitoring (SiO_2, 25 % ethyl acetate in hexanes) showed complete disappearance of starting material and the appearance of a new yellow spot (R_f = 0.27, UV visualization). Processing of the reaction mixture as for 8a (this section above) and chromatography (flash SiO_2, 7 × 3/4 in., 0% then 40% ethyl acetate in hexanes) gave 24 mg (40%) of product as a yellow solid whose spectroscopic data were consistent with the enolic form of the β-keto ester: mp 83–85 °C (dichloroethane and pentane); IR (KCl cells, CH_2Cl_2, cm^{-1}) 1774, 1741, 1655, 1628; ^1H NMR (300 MHz, $CDCl_3$, enol form) δ 6.35 (s, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.06 (m, 2 H), 3.96 (m, 2 H), 1.74 (m, 6 H), 1.56 (s, 1H), 1.30 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.6, 185.9, 181.9, 176.3, 155.3, 145.6, 129.5,

76.6, 53.3, 49.2, 26.1, 25.6, 22.8, 18.0. Anal. Calcd for $C_{14}H_{17}O_5N$: C, 60.19; H, 6.14; N, 5.02. Found: C, 60.11; H, 6.15; N, 4.96.

3-(2-Hydroxybenzoyl MEM ether)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8g). Salicylic acid MEM ether (48 mg, 0.21 mmol) was dissolved in CH_2Cl_2, and Ghosez' reagent[47] (29 μL, 0.21 mmol) was added. After stirring for 4 h, the solvent and excess reagent were removed in vacuo (25 °C at 10^{-3} mmHg). The oily residue was taken up in 4 mL of THF and 3-(tri-*n*-butylstannyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione, **2** (95 mg, 0.21 mmol), benzylchlorobis(triphenylphosphine)palladium (3 mg, 2 mol%), copper iodide (1 mg, 2 mol%), and BHT (1 mg, 2 mol%) were added. The reaction mixture was stirred at room temperature and monitored by TLC (SiO_2, 20% ethyl acetate in hexanes followed by 50% ethyl acetate in hexanes). After 3 h the reaction mixture was partitioned between acetonitrile (20 mL) and hexanes (30 mL). The CH_3CN layer was washed with hexanes (3 × 30 mL) and concentrated, and the product was isolated by chromatography (Chromatotron, SiO_2, 40% ethyl acetate in hexanes) giving 55 mg (70%) of **8g** as an orange oil: IR (CH_2Cl_2, cm^{-1}) 1780, 1770, 1640, 1618; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.44 (m, 2H), 7.36–7.27 (m, 1H), 7.12–7.05 (m, 1H), 5.21 (s, 2 H), 4.07 (m, 2 H), 3.96 (m, 2 H), 3.76 (m, 2 H), 3.51, (m, 2 H), 3.34 (s, 3 H), 1.88–1.70 (m, 6 H); ^{13}C NMR (75.1 MHz, $CDCl_3$) δ 197.5, 185.8, 184.5, 176.4, 158.3, 157.1, 134.2, 130.0, 128.5, 121.7, 115.1, 94.5, 71.4, 67.8, 58.9, 52.9, 49.9, 26.5, 25.9, 23.3. Anal. Calcd. for $C_{20}H_{23}O_6N$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.28; H, 6.20; N, 3.76.

Palladium-Catalyzed Acetylation of 3. 3-Benzoyl-4-(4-morpholinyl)-3-cyclobutene-1,2-dione (9a). 3-(4-Morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**3**) (109 mg, 0.24 mmol), benzoyl chloride (31 μL, 0.24 mmol), benzylchlorobis(triphenylphosphine)palladium (4 mg, 2.5 mol%), and CuI (1 mg, 2.5 mol%) were dissolved in 5 mL of CH_3CN and heated to 50 °C for 1 h with monitoring by TLC (SiO_2, 50% ethyl acetate in hexanes) showing product as a yellow, UV active spot (R_f = 0.50). The reaction was cooled, diluted with acetonitrile (30 mL) and washed with hexanes (3 × 30 mL), and 55 mg (78%) of the product was isolated as a yellow solid via chromatography (Chromatotron, SiO_2, 2 mm, 30% ethyl acetate in hexanes): mp 132–133 °C (dichloroethane and pentane); IR (KCl cell, CH_2Cl_2, cm^{-1}) 1782, 1761, 1642, 1616; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2 H), 7.67–7.59 (m, 1 H), 7.56–7.47 (m, 2 H), 4.18 (m, 2 H), 3.96 (m, 2 H), 3.87 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.8, 186.6, 184.1, 178.7, 157.6, 136.2, 134.3, 129.8, 128.6, 66.7, 66.4, 51.0, 48.6. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.35; H, 4.84; N, 5.14.

3-(2-Acetoxybenzoyl)-4-(4-morpholinyl)-3-cyclobutene-1,2-dione (9b). 3-(4-Morpholinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**3**) (109, mg, 0.24 mmol), 2-acetoxybenzoyl chloride (48 mg, 0.24 mmol), benzylchlorobis(triphenylphosphine)palladium (3.6 mg, 2.5 mol%), and CuI (1 mg, 2.5 mol%) were stirred at room temperature in 5 mL of THF for 2 h until TLC monitoring (SiO_2, 50% ethyl acetate in hexanes) showed one new yellow spot (R_f = 0.30, UV visualization). The reaction was processed as for **9a** above and chromatographed (flash SiO_2, 8 × 0.75 in., 40% ethyl acetate in hexanes) giving 57 mg (73%) of product as a yellow solid: mp 172–173 °C (dichloroethane and pentane); IR (KCl cell, CH_2Cl_2 cm^{-1}) 1782, 1763, 1647, 1618; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.76 (m, 1 H), 7.65–7.57 (m, 1 H), 7.43–7.35 (m, 1 H), 7.20–7.13 (m, 1 H), 4.16 (m, 2 H), 3.90 (m, 2 H), 3.86 (m, 4 H), 2.24 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.3, 184.7, 183.8, 177.9, 169.3, 157.0, 149.1, 134.4, 131.3, 129.5, 126.0, 123.4, 66.8, 66.4, 51.6, 48.5, 20.9. Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.0; H, 4.59; N, 4.05. Found: C, 62.10; H, 4.34; N, 4.05.

Palladium-Catalyzed Acylation of 4. 3-Amino-4-benzoyl-3-cyclobutene-1,2-dione (10a). 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**4**) (148 mg, 0.40 mmol), benzoyl chloride (47 μL, 0.40 mmol), and a 1:1 mol ratio of benzylchlorobis(triphenylphosphine)palladium (7.6 mg, 2.5 mol%) and CuI (1.9 mg, 2.5 mol%) were stirred in THF at 50 °C with formation of a yellow precipitate within 5 min. After 20 min, TLC (SiO_2, 30% ethyl acetate in hexanes) indicated consumption of starting material. The reaction mixture was cooled and the precipitate collected on a medium porosity fritted funnel and washed with hexanes (3 × 10 mL). The precipitate was dried in vacuo leaving 68 mg (84%) of a bright yellow solid: mp 257 °C dec (acetone and pentane); IR (KBr, cm^{-1}) 3350, 3208, 1782, 1658, 1650; ^1H NMR (300 MHz, acetone-d_6) δ 10.10 (br s, 1 H), 9.60 (br s, 1 H), 8.45–8.35 (m, 2 H), 7.72–7.62 (m, 1 H), 7.62–7.51 (m, 2 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 198.3, 185.3, 184.4, 184.0, 155.6, 135.9, 133.8, 128.9, 128.6. Anal. Calcd for $C_{11}H_7NO_3$: C, 65.66; H, 3.51; N, 6.97. Found: C, 65.58; H, 3.54; N, 6.94.

3-Amino-4-((*E*)-2-butenoyl)-3-cyclobutene-1,2-dione (10b). 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**4**) (220 mg, 0.57 mmol), crotonyl chloride (55 μL, 0.57 mmol), and a 1:1 mol ratio of benzylchlorobis(triphenylphosphine)palladium (10.8 mg, 2.5 mol%) and CuI (2.7 mg, 2.5 mol%) were stirred in THF at 50 °C for 15 min until TLC monitoring (SiO_2, 30% ethyl acetate in hexanes) showed a new yellow spot (R_f = 0.30, UV visualization). Solvent was evaporated, the green residue was taken up in CH_3CN (20 mL) and washed with hexanes (3 × 20 mL), the CH_3CN layer was concentrated, and 88 mg (93%) of product was isolated as a yellow solid by chromatography (flash SiO_2, 6 × 0.75 in., 30% ethyl acetate in hexanes): mp 160–161 °C (acetone and pentane); IR (CH_2Cl_2, cm^{-1}) 3470, 3350, 1788, 1774, 1647, 1636; ^1H NMR (300 MHz, acetone-d_6) δ 8.90 (br s, 1 H), 8.50 (br s, 1 H), 7.41 (dq, J = 6.9, 15.8 Hz, 1 H), 6.51 (dd, J = 1.6, 15.8 Hz, 1 H), 1.94 (dd, J = 1.6, 6.9 Hz, 3 H); ^{13}C NMR (75.1 MHz, DMSO-d_6) δ 198.5, 185.8, 182.9, 183.1, 155.8, 146.1, 130.1, 18.2. Anal. Calcd for $C_8H_7NO_3$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.03; H, 4.31; N, 8.43.

3-Amino-(4-methoxybenzoyl)-3-cyclobutene-1,2-dione (10c). 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**4**) (149 mg, 0.39 mmol), *p*-anisoyl chloride (66 mg, 0.39 mmol), and a 1:1 mol ratio of benzylchlorobis(triphenylphosphine)-palladium (7.4 mg, 2.5 mol%) and CuI (1.8 mg, 2.5 mol%) were stirred in THF at 50 °C for 20 min with TLC monitoring (SiO_2, 30% ethyl acetate in hexanes). The yellow precipitate which had formed was collected on a fine porosity fritted funnel, and washed with hexanes (3 × 30 mL), CH_2Cl_2 (3 × 10 mL), and then cold acetone (1 × 10 mL). The solid was dissolved in hot acetone and filtered while hot. The filtrate was concentrated and dried in vacuo yielding 81 mg (97%) of a bright yellow solid: mp 258 °C dec (acetone and pentane); IR (KBr, cm^{-1}) 3340, 3180, 1779, 1758, 1658; ^1H NMR (300 MHz, DMSO-d_6) δ 9.80 (br s, 1 H), 9.30 (br s, 1 H), 8.12 (d, J = 8.1 Hz, 2 H), 7.05 (d, J = 8.1 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 197.9, 184.6, 184.2, 183.8, 163.8, 156.4, 131.5, 128.9, 114.0, 55.5. Anal. Calcd. for $C_{12}H_9NO_3$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.07; H, 3.89; N, 6.02.

3-Acrylyl-4-amino-3-cyclobutene-1,2-dione (10d). 3-Amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**4**) (165 mg, 0.45 mmol), acrylyl chloride (36 μL, 0.45 mmol), and a 1:1 mol ratio of benzylchlorobis(triphenylphosphine)palladium (7.4 mg, 2.5 mol%) and CuI (1.8 mg, 2.5 mol%) were stirred in 4 mL of THF at 50 °C for 15 min with monitoring by TLC (SiO_2, 30% ethyl acetate in hexanes). The reaction was cooled and the solvent was evaporated leaving an orange-yellow solid that was triturated with CH_2Cl_2 and filtered. The solid was washed with CH_2Cl_2 (3 × 20 mL) and then taken up in 10 mL of acetone and dried in vacuo yielding 36 mg (53%) of a yellow solid: mp 156 °C (acetone and pentane); IR (KBr, cm^{-1}) 3315, 3212, 1787, 1776, 1659, 1641, 1605; ^1H NMR (300 MHz, acetone-d_6) δ 9.00 (br s, 1 H), 8.60 (br s, 1 H), 6.79, (d, J = 7.5 Hz, 1 H), 6.78 (d, J = 4.5 Hz, 1H), 6.08 (dd, J = 4.5, 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 198.5, 185.7, 183.5, 183.0, 154.9, 134.7, 131.1. Anal. Calcd for $C_7H_5NO_3$: C, 55.62; H, 3.34; N, 9.27. Found, C, 55.30; H, 3.64; N, 8.63.

3-(2-Acetoxybenzoyl)-4-amino-3-cyclobutene-1,2-dione (10e). 2-Acetoxybenzoyl chloride (272 mg, 1.37 mmol), 3-amino-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (**4**) (530 mg, 1.37 mmol), benzylchlorobis(triphenylphosphine)palladium (20 mg, 2 mol%), copper iodide (5 mg, 2 mol%), and BHT (6 mg, 2 mol%) were stirred at room temperature in THF (20 mL) for 2 h. The solvent was evaporated and the dark brown residue was partitioned between CH_3CN (40 mL) and hexanes (20 mL). The CH_3CN layer was washed with three portions of hexanes and then concentrated and chromatographed (Chromatotron, SiO_2, 2 mm thickness, 30% ethyl acetate in hexanes) giving a yellow band

(47) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 5, 282.

that was collected and recrystallized (1,2-dichloroethane and pentane) to afford 218 mg (62%) of yellow crystals: mp 143–144 °C dec (analytical sample from acetone and pentane); IR (KCl cell, CH_2Cl_2, cm^{-1}) 3463, 3351, 1784, 1771, 1647, 1607; ^1H NMR (300 MHz, DMSO-d_6) δ 9.82 (br s, 1 H), 9.45 (br s, 1 H), 8.07–8.00 (m, 1 H), 7.70–7.60 (m, 1 H), 7.47–7.39 (m, 1 H), 7.28–7.20 (m, 1 H), 2.19 (s, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 199.3, 184.6, 184.51, 184.1, 169.2, 155.9, 149.1, 134.4, 131.5, 129.5, 126.2, 124.0, 21.1. Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.41. Found: C, 60.14; H, 3.49; N, 5.37.

Palladium-Catalyzed Carbonylative Cross-Coupling of 2 and Iodobenzene. 3-Benzoyl-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (8a). 3-(1-Piperidinyl)-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (2) (128 mg, 0.28 mmol), iodobenzene (0.031 mL, 0.28 mmol), benzylchlorobis(triphenylphosphine)-palladium (5.3 mg, 2.5 mol%), and CuI (1.3 mg, 2.5 mol%) were dissolved in 3 mL of THF in a dried flask which was filled with CO. The reaction mixture was heated at 50 °C under 1 atm CO for 40 h with monitoring by TLC (SiO_2, 30% ethyl acetate in hexanes). The reaction mixture was allowed to cool, the solvent was evaporated, and the residue was taken up in 15 mL of acetonitrile and extracted with hexanes (3 × 15 mL). The combined hexanes layers were back-extracted with 10 mL of acetonitrile and the combined acetonitrile solutions were concentrated and 49 mg (65%) of the product isolated by chromatography (Chromatotron, SiO_2, 2 mm, 30% ethyl acetate in hexanes) as a yellow solid. Physical data listed above.

Palladium-Catalyzed Acylations of Acetal 11. 3-Benzoyl-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12a. Acetal 11 (0.234 g, 0.536 mmol) and 0.081 g of benzoyl chloride were dissolved in 2.0 mL of CO-saturated benzene. $(C_6H_5CH_2)$-$ClPd(PPh_3)_2$ (0.004 g, 1 mol%) was added and the reaction mixture was heated to 80 °C under 1 atm CO for 24 h. The reaction mixture was allowed to cool, diluted with 15 mL of Et_2O, washed with 10% aqueous KF (3 × 10 mL), and filtered through SiO_2 (1 × 3 in.) with Et_2O. The solvents were removed on a rotary evaporator and vacuum pump, and the mixture was purified by chromatography (Chromatotron, 2-mm SiO_2 rotor, 20–40% Et_2O in hexanes) to yield 0.103 g (78%) of **12c** as a yellow solid: mp 83–85 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 1787, 1662, 1604; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2 H), 7.70–7.63 (m, 1 H), 7.57–7.50 (m, 2 H), 4.20–4.00 (m, 4 H), 1.98 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.7, 189.5, 171.7, 162.6, 135.5, 133.9, 128.7, 128.3, 120.5, 65.8, 9.09. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.71; H, 5.03.

3-(*p*-Methoxybenzoyl)-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12b. Prepared analogously to **12a** in 92% yield (0.135 g from 0.234 g of 11 and 0.101 g of *p*-anisoyl chloride) as a yellow solid: mp 83–84.5 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 1780, 1649, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (app d, J = 8.9 Hz, 2 H), 7.01 (app d, J = 8.9 Hz, 2 H), 4.17–4.01 (m, 4 H), 3.91 (s, 3 H), 1.97 (s, 3 H). Anal. Calcd for $C_{15}H_{15}O_5$: C, 65.69; H, 5.14. Found: C, 65.52; H, 5.21.

3-Acetyl-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12c. Prepared analogously to **12a** in 68% yield (0.067 mg from 0.230 g of acetal 11 and 0.050 g of acetyl chloride) as an orange oil: IR (CH_2Cl_2, cm^{-1}) 1778, 1693; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (br s, 4 H), 2.43 (s, 3 H), 2.12 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.8, 193.4, 166.2, 164.8, 118.7, 65.9, 29.6, 9. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.43; H, 5.57.

3-Isobutyryl-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12d. Prepared analogously to **12a** in 64% yield (0.072 g from 0.234 g of 11 and 0.063 g of *i*-butyryl chloride) as a yellow solid: mp 40–42 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 1780, 1687, 1621; ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (br s, 4 H), 2.89 (hept, J = 6.9 Hz, 1 H), 2.08 (s, 3 H), 1.17 (d, J = 6.9 Hz, 6 H). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85:H, 6.71. Found: C, 62.76; H, 6.72.

Palladium-Catalyzed Carbonylative Cross-Couplings of 11. 3-Benzoyl-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12a. Acetal 11 (0.230 g, 0.536 mmol) and 0.132 g (0.649 mmol) of iodobenzene were dissolved in 2.0 mL of CO-saturated benzene in a Griffin–Worden pressure vessel. $(C_6H_5CH_2)ClPd(PPh_3)_2$ (0.0043 g, 1 mol%) was added and the reaction mixture was placed under 32 psi of CO. The solution was heated to 80 °C for a period of 18 h. The reaction mixture was allowed to cool and the pressure released. The solution was diluted with 15 mL of Et_2O, washed with 10% aqueous KF (3 × 15 mL), and filtered through SiO_2 (1 × 4 in.) with Et_2O. The solvents were removed on a rotary evaporator and vacuum pump, and the product was purified by chromatography (Chromatotron, 2-mm SiO_2 rotor, 20% Et_2O in hexanes) to afford 0.113 g (86%) of **12a** with the same physical properties described above.

3-(*p*-Methoxybenzoyl)-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12b. Prepared analogously to **12a** in this section in 81% yield (0.208 g from 0.409 g of acetal 11 and 0.264 g of *p*-iodoanisole) as a yellow solid with the same physical properties as described above.

3-(2-Thienylcarbonyl)-4-methyl-3-cyclobutene-1,2-dione 2-(Ethylene acetal), 12e. Prepared analogously to **12a** in this section in 53% yield (0.179 g from 0.585 g of acetal 11 and 0.342 g of 2-iodothiophene) as an orange oil: IR (CH_2Cl_2, cm^{-1}) 1783, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 1.0, 3.8 Hz, 1 H), 7.83 (dd, J = 1.0, 4.9 Hz, 1 H), 7.21 (dd, J = 3.8, 4.9 Hz, 1 H), 4.24–4.10 (m, 4 H), 2.08 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.0, 180.4, 169.7, 163.7, 142.9, 136.2, 134.7, 128.2, 120.0, 65.7, 9.1. Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03. Found: C, 57.71; H, 4.07.

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