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Pd-Catalyzed, Cu(I)-Mediated Cross-Couplings of Bisarylthiocyclobutenediones with Boronic Acids and Organostannanes

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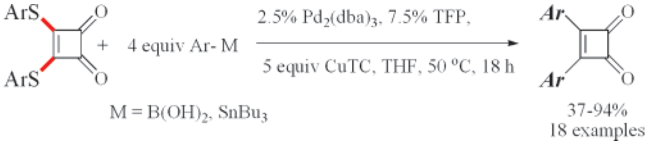
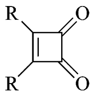


Bisarylthiocyclobutenedione **7** reacted smoothly with a variety of both organostannanes and (hetero)arylboronic acids in the presence of a catalytic amount of Pd and a stoichiometric amount of CuTC to produce symmetrical disubstituted cyclobutenediones in yields that range from 37 to 94% (18 examples).

Over the last three decades, various research groups have demonstrated the remarkable versatility of cyclobutenedione **1** and squaric acid ester derivatives **2** in the synthesis of organic compounds. In particular, the groups of Liebeskind,[1] Moore,[2] Paquette,[3] and Danheiser[4] have been very active in this area.



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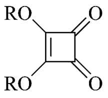

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Starting from either **1** or **2**, a wide variety of different compounds have been prepared, including triquinanes **3**,[3a] angularly fused aromatic systems **4**,[5] bisquaryls **5**,[6] and 2-pyrones **6**[7] just to mention a few (Figure 1).

Squaric acid derivatives have also been used as ion sensors[8] and ligands[9] and to prepare cyclo[*n*]carbons.[10]

Accordingly, the need for new protocols that allow for a practical functionalization of the 3 and 4 positions becomes evident.

To date, there are several reports in the literature describing the introduction of simple alkyl, aryl, heteroaryl, alkynyl, and alkenyl[11] functional groups in those positions of cyclobutenedione. However, they require the use of highly reactive Grignard or organolithium derivatives which limits the functional groups that can withstand these reaction conditions. Few milder transition-metal-mediated methods to prepare such derivatives have been reported. Namely, Knochel et al. reported the reaction of 3,4-dichlorocyclobutendione and zinc−copper reagents.[12] Likewise, Liebeskind disclosed an efficient synthesis of 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione. This stannylcyclobutenedione underwent cross-couplings with organic iodides and triflates catalyzed by the $PhCH_2ClPd(PPh_3)_2/CuI$ system.[1k,6,13] The same group reported the Stille couplings of monohalocyclobutenediones with organostannanes.[14]

Against this background, we decided to explore the use of the palladium-catalyzed, copper-mediated cross-couplings of thioorganics with both organostannanes and boronic acids[15] to develop a mild protocol to functionalize the vinyl positions of cyclobutenedione with both aryl and heteroaryl groups.

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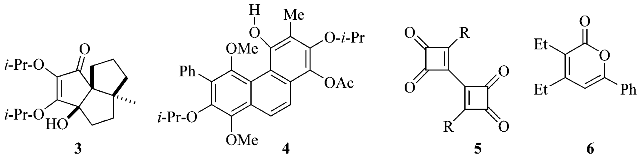


FIGURE 1. Examples of organic compounds prepared from either **1** or **2**.

SCHEME 1. Synthesis of Thiocyclobutenediones 7−9

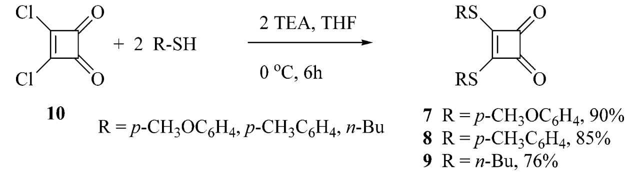
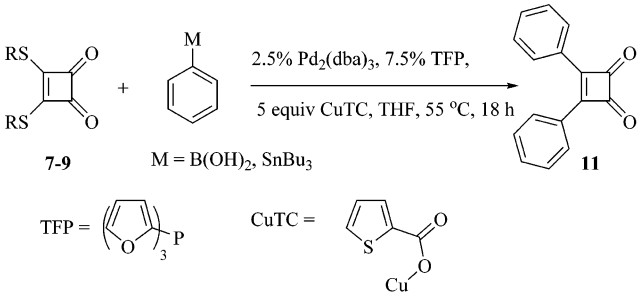


TABLE 1. Reactivity of Thiocyclobutenediones 7−9 in the Liebeskind−Srögl Cross-Coupling



entry	M	R	% yield of **11**[a]
1	B(OH)$_2$	*p*-MeOC$_6$H$_4$	70
2	B(OH)$_2$	*p*-MeC$_6$H$_4$	62
3	B(OH)$_2$	*n*-Bu	trace amt
4	SnBu$_3$	*p*-MeOC$_6$H$_4$	61
5	SnBu$_3$	*p*-MeC$_6$H$_4$	51
6	SnBu$_3$	*n*-Bu	trace amt

[a] Isolated yield.

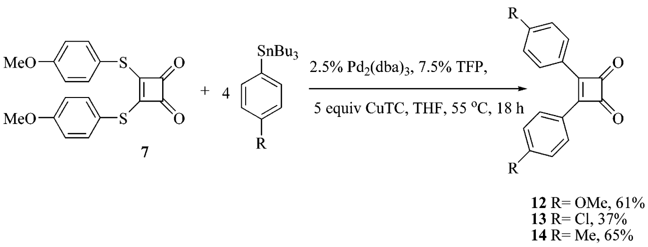
Bisthiocyclobutenediones **7**−**9** where prepared in order to study the influence of the substituent on sulfur in the cross-couplings. Thus, the corresponding thiols were reacted with 3,4-dichlorocyclobutene-1,2-dione[16] **10** in the presence of triethylamine (Scheme 1).

Thiocyclobutenediones **7**−**9** were obtained in a straightforward manner as stable yellow powders which could be handled in air with no evident signs of decomposition even after several weeks. With **7**−**9** in hand, their reactivity was assessed with phenylboronic acid and with tributylphenylstannane as illustrated in Table 1. Since thiocyclobutenediones **7**−**9** may be regarded as vinylogous thiol esters, the initial reactions conditions chosen were based upon those reported for the cross-couplings of thiol esters with organostannanes and boronic acids.[15b,i]

Aromatic substituents on sulfur gave the best results presumably because once the oxidative addition takes place, the negative charge on sulfur may be better stabilized onto the aromatic ring. Due to its ease of formation, excellent shelf life, and higher reactivity in the cross-couplings, thiocyclobutenedione **7** was chosen as the starting material for the reaction with boronic acids and organostannanes.

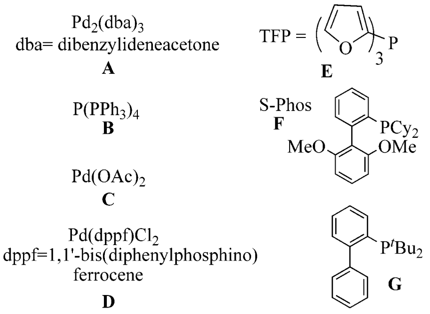
Even though the aim of this report is to emphasize the scope of the cross-coupling reaction with boronic acids by virtue of their availability and nontoxicity, a few organostannanes were surveyed (Scheme 2).

SCHEME 2. Short Survey of Organostannanes in the Liebeskind−Srögl Cross-Coupling



It was necessary to use a 2-fold excess of the stannane to compensate for the formation of the homocoupled biaryl byproduct present in all of these reactions. The yields for electron-rich substituents (OMe, Me) were moderate. The *p*-Cl derivative was somewhat unstable to aqueous saturated KF treatment[17] to eliminate the tin byproducts, hence its low yield. As in the majority of cross-couplings reactions where organostannanes are involved, the removal of tin byproducts was tedious and time-consuming. Thus, the need for a better and more practical procedure became clear.

We then turned our attention to explore the scope of the reaction with boronic acids. The reaction was first optimized by varying the reaction conditions as shown in Table 2. The Pd sources and external ligands used are shown below.



Initial testing with a slight excess of the boronic acid only produced incomplete conversions and rather complex crude mixtures (entries 1−5) using a variety of Pd sources and external ligands in THF at 55 °C. The formation of **16** was never avoided even with rigorous deoxygenation and slow addition of the boronic acid. Addition of an increased amount of boronic acid to compensate for the formation of the homocoupled byproduct **16** showed improvement only when used in the presence of Pd(PPh$_3$)$_4$ in THF (entry 7). Complete conversion and a 69% yield of **14** were obtained. Finally, similar results were observed with either Pd$_2$(dba)$_3$/TFP or Pd(PPh$_3$)$_4$ in THF when 4 equiv of the boronic acid were added (entries 8 and 9). In light of the slightly higher efficiency displayed (77% vs 75%) and better shelf life, the combination Pd$_2$(dba)$_3$/TFP was chosen to study the scope and limitations of the reaction. The results are summarized in Table 3.

In general, the reaction furnished the desired products with boronic acids containing strong electron-donating groups (entries 3, 6, and 7) in moderate to good yields. Arylboronic acids with milder electron donors (entries 1, 4, 5, and 10) gave the corresponding disubstituted cyclobutenediones in moderate

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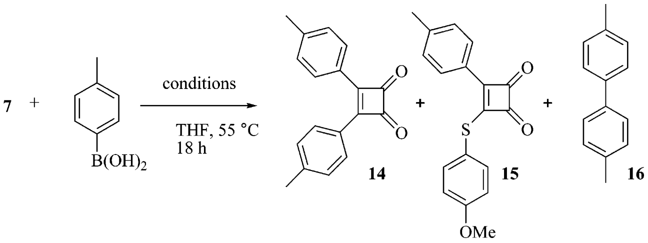
TABLE 2. Optimization of the Cross-Coupling of 7 with $MeC_6H_4B(OH)_2$

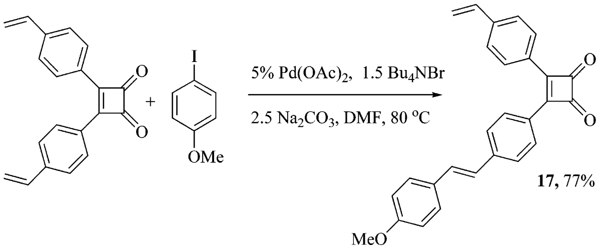


entry	% Pd	% PR_3	$RB(OH)_2$[a] (equiv)	result[b]
1	2.5% **A**	7.5% **E**	2.5	similar amounts of **7**, **14**, **15**, and **16** were observed
2	2.5% **D**		2.5	as in entry 1
3	5% **B**		2.5	1:1 (**7:14**)
4	2.5% **C**	5% **F**	2.5	similar amounts of **7**, **14**, and **15**
5	5% **A**	5% **G**	2.5	only **7** and **16** were observed
6	5% **D**		3.0	complex mixture
7	5% **B**		3.0	**14** (69%) + traces of **16**
8	2.5% **A**	7.5% **E**	4.0	**14** (77%) + traces of **16**
9	5% **B**		4.0	**14** (75%) + traces of **16**

[a] A 25% excess of CuTC was used with respect to the boronic acid. [b] The results were obtained from the ^{1}H NMR spectrum of the crude material.

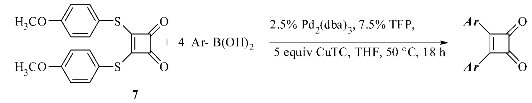
yields. Boronic acids with electron-withdrawing substituents (entries 2, 11, 12, and 14) also reacted smoothly to give the desired products in acceptable yields. The heteroaryl boronic acids evaluated in this study displayed variable behavior. For reasons that are not clear at the moment, 3-pyridylboronic failed to react under the standard conditions. Variations that included the use of $Pd(PPh_3)_4$ and the addition of an additive ($Zn(OAc)_2$) failed as well.[15i] Dibenzofurylboronic acid (entry 15) produced the expected product albeit in low yield. The fact that in this case all of the starting material is consumed, suggests a degree of instability of the final product. 3-Thienylboronic acid (entry 13) gave the product in excellent yield. Ferrocenylboronic acid showed good reactivity and gave the product in 71% yield (entry 7).

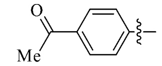
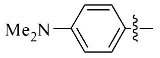
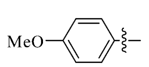
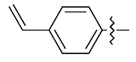
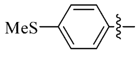
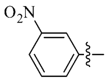
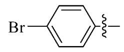
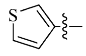
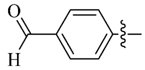
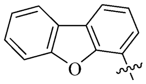
It is worth mentioning that the products of entries 9 and 12, since they bear either a vinyl group or a Br atom in the para position of the aromatic ring, respectively, can participate in further Pd-catalyzed cross-coupling reactions, thereby yielding more elaborate derivatives. As an example, bis(*p*-styryl)-cyclobutenedione was reacted with *p*-iodoanisole under Heck conditions[18] to give monofunctionalized product **17** in 77% yield (eq 1).



(1)

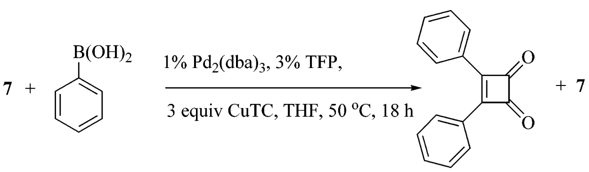
TABLE 3. Scope and Limitations of the Liebeskind−Srögl Cross-coupling



Entry	Hetero(Aryl)	% yld[a]
1	C_6H_5-	70
2		66
3		76
4	*p*-tolyl-	77
5	*m*-tolyl-	56
6		84
7	Ferrocenyl-	71
8	3-pyridyl-	n.r.
9		44
10		42
11		58
12		61
13		94
14		76
15		37

[a] Isolated yield after column chromatography.

Finally, our efforts focused on the possibility of synthesizing nonsymmetric cyclobutenediones. Attempts to cross-couple **7** with 1 equiv of phenylboronic acid to introduce only one phenyl group failed, giving the disubstituted product and unreacted **7** (eq 2).



(2)

In conclusion, we have developed a mild and efficient method to incorporate aryl, heteroaryl, and organometallic functional groups at the vinylic positions of cyclobutenedione under mild and nonbasic reaction conditions. Some of these derivatives would be difficult to obtain using the reported methods to functionalize cyclobutenediones. Even though Knochel's organocuprate method allows the introduction of two different groups at the vinyl positions, the methodology presented here uses readily available reagents and catalysts that are air stable. Bisthiocyclobutenedione **7** reacts smoothly with both arylstannanes and (hetero)arylboronic acids to furnish the corresponding symmetric cyclobutenediones in modest to excellent yields.[19] Limitations of this methodology include the failed reaction with

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(18) Reiser, O.; Reichow, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1277.

pyridylboronic acid and the inability to synthesize nonsymmetrical derivatives. Further studies of the reactivity of **7** toward alkylboronic acids and other unsaturated boronic acids and organostannanes (vinyl, alkynyl, allyl, etc.), as well as with organozinc, organocopper, and organomagnesium derivatives are being currently pursued in our laboratory and will be reported in due course.

Experimental Section

3,4-Bis(*p*-methoxythiophenoxy)-3-cyclobutene-1,2-dione 7. To a cool (0 °C) THF (10 mL) solution of dichlorodione **10** (250 mg, 1.6 mmol) was added *p*-methoxythiophenol (0.4 mL, 3.3 mmol) dropwise via syringe under N_2, followed by the addition of triethylamine (0.43 mL, 3.3 mmol). The reaction mixture gradually reached 25 °C and after 6 h was quenched with an equivalent volume of aq NH_4Cl. Then, it was extracted with CH_2Cl_2 (3 × 30 mL), dried (anhyd $MgSO_4$), and filtered. The solvent was removed in vacuo to give a yellow solid. The remaining solid was triturated in hexanes and used directly in the following reactions (515 mg, 90%). For characterization purposes, the product was crystallized from hexane/EtOAc: TLC ($R_f = 0.3$, silica gel, 20% EtOAc/hexane); mp 133 °C; IR (KBr) 2939 (m), 2840 (m), 2366 (m), 1787 (s), 1807 (m) 1761 (s), 1740 (m), 1590 (s), 1571 (s); ^1H NMR (200 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.94$ Hz, 2H), 6.90 (d, $J = 8.89$ Hz, 2H), 3.80 (s, $J = 1.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 188.2, 186.7, 161.7, 136.4, 115.0, 66.1, 55.7. Anal. Calcd for $C_{18}H_{14}O_4S_2$: C, 60.32; H, 3.94; S, 17.89. Found: C, 59.99; H, 3.92; S, 17.58.

Typical Experimental Procedure for the Cross-Coupling Reactions with Organostannanes. Synthesis of Dione 14. A 50 mL Schlenk flask under N_2 was charged with **7** (25.0 mg, 0.07 mmol, 1 equiv), tributyl-*p*-tolylstannane (106.0 mg, 0.28 mmol, 4 equiv), and anhyd THF (5 mL). The resulting solution was deoxygenated by bubbling N_2 for 10 min. Then $Pd_2(dba)_3$ (1.6 mg, 1.7×10^{-3} mmol), trifurylphosphine (1.2 mg, 5.2×10^{-3} mmol), and CuTC (66.6 mg, 0.35 mmol) were added, and the reaction mixture was heated to 50 °C for 18 h. The heating bath was removed, and the volatiles were eliminated in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, ethyl acetate/hexanes gradient) to give the products as yellow solids. The remaining tin impurities were removed by partitioning the product between MeCN (2 mL) and hexanes (2 mL) and washing the MeCN phase with fresh hexanes (5 × 2 mL). The MeCN was removed in vacuo to give the pure product (yellow solid, 12.0 mg, 65%): TLC (30% EtOAc/hexanes, $R_f = 0.75$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, $J = 7.0$ Hz, 2H), 7.36 (d, $J = 7$ Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 196.6, 186.8, 144.6, 130.2, 128.5, 125.9, 22.2; MS (EI) *m/z* calcd 262, found 262.[21]

Typical Experimental Procedure for the Cross-Coupling Reactions with Boronic Acids. Synthesis of 3,4-Bis(3-thienyl)-3-cyclobuten-1,2-dione. A 50 mL Schlenk flask under N_2 was charged with **7** (35 mg, 0.098 mmol, 1 equiv), 3-thienylboronic acid (50 mg, 0.4 mmol, 4 equiv), and anhyd THF (5 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. Then, CuTC (93 mg, 0.5 mmol, 5 equiv), $Pd_2(dba)_3$ (2.3 mg, 2.4×10^{-3} mmol), and trifurylphosphine (1.8 mg, 7.3×10^{-3} mmol) were added. The reaction mixture was heated to 55 °C for 18 h, the heating bath was removed, and the volatiles were eliminated in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, ethyl acetate/hexanes gradient) to give the product as a yellow solid (22.6 mg, 94%): TLC (30% EtOAc/hexanes, $R_f = 0.7$); mp = 149−150 °C; IR (KBr, cm^{-1}) 1754.8 (s), 1569.3 (s), 1514.8 (m), 1437.8 (m), 1221.1 (m), 1124.0 (m); ^1H NMR (200 MHz, $CDCl_3$) δ 8.58 (dd, 1.4 Hz, $J = 1.2$ Hz, 1H), 7.78 (dd, $J = 1.0$, 1.0 Hz, 1H), 7.58 (dd, $J = 3.0$, 2.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.8, 178.4, 132.6, 129.6, 128.0, 126.3; HRMS ($C_{12}H_6O_2S_2$) calcd 245.9809, found 245.9813.

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Supporting Information Available: Experimental procedures and compound characterization data and copies of the NMR spectra of the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) After a reviewer's suggestion, dichlorocyclobutenedione **10** was reacted with *p*-tolylboronic acid under the Suzuki conditions (1% $Pd(OAc)_2$, 2.5% S-Phos, 2 equiv of K_3PO_4, toluene, 90 °C).[20] However, only traces of **18** were observed.

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