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Selective Cross-Couplings. Sequential Stille–Liebeskind/Srogl Reactions of 3-Chloro-4-arylthiocyclobutene-1,2-dione

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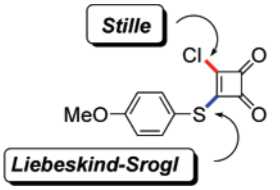
ABSTRACT



2

The synthesis and initial reactivity studies of 2 are described. It was found that it participates in Stille couplings exclusively at the C–Cl site with a number of organostannanes (58–71% yield) in the absence of Cu(I). Then, these new derivatives were functionalized at the C–S site with boronic acids by switching to the Liebeskind–Srogl reaction conditions (in the presence of a Cu(I) carboxylate) to yield the bifunctionalized cyclobutenediones (44–90% yield).

The synthetic utility of cyclobutenedione derivatives **1** has been extensively demonstrated.[1] These types of compounds have been used not only to prepare organic molecules with biological relevance but also as ion sensors,[2] as ligands,[3] and to prepare cyclo[*n*]carbons.[4] One of the main features that makes cyclobutenediones such a useful starting material is the fact that the four-membered ring is a latent highly substituted benzene **1a** or quinone ring system **1b** (Figure 1). In doing so, from the reactivity point of view, **1** goes from being an electron-deficient fragment to an electron-rich moiety (**1**→**1a**).

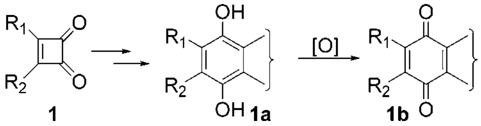


Figure 1. Cyclobutenediones as latent aromatic or quinoid rings.

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[2] Frontera, A.; Orell, M.; Garau, C.; Quiñonero, D.; Molins, E.; Mata, I.; Morey, J. *Org. Lett*. **2005**, *7*, 1347.

[3] Murakami, H.; Minami, T.; Osawa, F. *J. Org. Chem*. **2004**, *69*, 4482.

[4] Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc*. **1990**, *112*, 1607.

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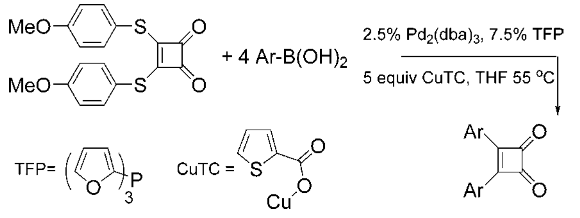
Thus, if both R_1 and R_2 are aryl substituents, this route would lead to the construction of tri- (or oligo-) phenylenes provided there is an efficient methodology to incorporate aryl fragments at the vinyl positions of **1**. Polyphenylenes are of significant importance in the design of organic light-emitting diodes (OLED's).[5] On the other hand, the terphenyl motif is found in a plethora of natural products.[6]

We have recently developed a mild functionalization of bisarylthiosubstituted cyclobutenediones using the Liebeskind−Srogl cross-coupling[7] to prepare bisferrocenylcyclobutenediones[8] and other symmetrical bisarylcyclobutenediones[9] (Scheme 1).

Scheme 1. Synthesis of Symmetrical Cyclobutenediones



Building upon our results, we wish to disclose the synthesis and initial synthetic applications of *3-chloro-4-arylthiocyclobutene-1,2-dione* 2 (Figure 2).

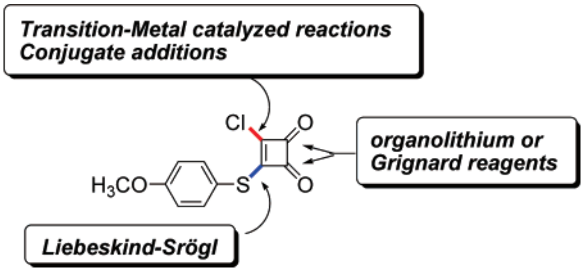
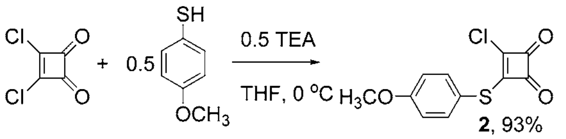


Figure 2. Multiple reaction centers of **2**.

Cyclobutenedione **2** displays three types of reaction centers. First, the Cl-bearing carbon atom may be regarded as part of either a vinyl chloride or a vinylogous acid chloride which can be functionalized by using the Stille, Suzuki, Heck, Sonogashira, Hiyama, or Negishi reaction,[10] among others, *provided no Cu(I) salts* or hydrolytic conditions are used (vide infra). Furthermore, **2** should presumably be susceptible to conjugate addition/elimination reactions of oxygen, nitrogen, or phosphorus nucleophiles and organocuprates. Second, the S-bearing vinyl carbon atom will react, as we have demonstrated,[9] with either boronic acids or organostannanes as long as a *Cu(I) carboxylate is used in stoichiometric amounts*. Third, the carbonyl groups react with Grignard or organolithium reagents as has been extensively shown in the classical ring-opening/expansion sequence that has been used to form benzene derivatives.[1]

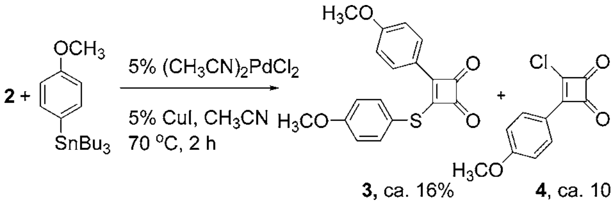
By the aforementioned arguments, **2** may become a very useful platform that possesses orthogonal reactivity because it can be functionalized *at will* at three different reaction centers by simply varying the reaction conditions.[11]

Cyclobutenedione **2** was prepared in 93% yield by treating 3,4-dichloro-3-cyclobutene-1,2-dione[12] with 0.5 equiv of *p*-methoxybenzenethiol and 0.5 equiv of triethylamine (eq 1).



(1)

Chlorothiocyclobutenedione **2** is a pale yellow solid with excellent shelf life. It can be handled in air with no special precautions, even after several months at room temperature, and it shows no signs of decomposition. Once **2** was prepared, we set forth studying its reactivity. On the grounds of handling a more robust product after the first cross-coupling, the Stille reaction was attempted first to introduce an aryl group at the Cl-bearing C atom. In this fashion, the resulting product would be stable to silica-gel chromatography purification. The initial reaction conditions used were similar to those that Liebeskind et al. applied for the Stille reaction of similar substrates with organostannanes,[13] i.e., a Pd(II) catalyst and CuI as a cocatalyst. However, the results were disappointing because a mixture of the arylated products at both the vinyl positions was observed in addition to unreacted **2** (eq 2).



(2)

These results, although not very useful from the synthetic point of view, strongly suggest that in the presence of Cu(I)

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(5) Li, Z. H.; Wong, M. S.; Tao, Y. *Tetrahedron* **2005**, *61*, 5277 and references cited therein.

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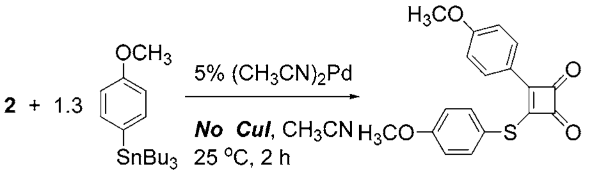
(8) Aguilar-Aguilar, A.; Peña-Cabrera, E.; Liebeskind, L. S. *ARKIVOC* **2004**, (*i*), 156.

(9) The results will be reported elsewhere.

(10) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 2004; Vols. 1−2.

(11) For an efficient example of orthogonal reactivity of thioorganics, see ref 7a.

both reactive centers (C−Cl and C−S) have comparable reactivity.[14] To achieve the sought after selectivity, CuI was eliminated from the initial Stille coupling reactions at the risk of compromising the reactivity of the vinyl chloride moiety (eq 3).

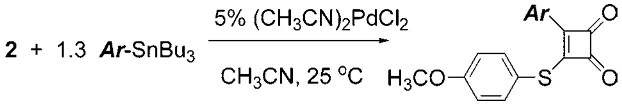


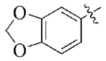
(3)

3, 69% sole product

To our delight, not only did the system show excellent reactivity even in the absence of CuI but also product **3** was obtained in 69% isolated yield at 25 °C. No evidence of any other cross-coupling product was observed in the ^{1}H NMR spectrum of the crude material. Thus, a series of arylstannanes were coupled with **2** under the reaction conditions of eq 3. The results are presented in Table 1.

Table 1. Stille Coupling of **2** with Organostannanes



entry	Ar	time (h)	compd	% yield[a]
1	*p*-$CH_3OC_6H_4$-	2	**3**	69
2	*p*-$CH_3C_6H_4$-	2	**5**	58
3	*p*-ClC_6H_4-	2	**6**	71
4		14	**7**	71

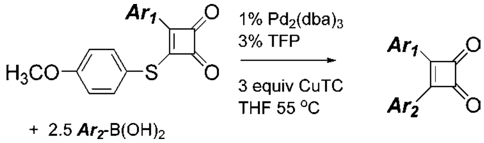
[a] Isolated yield.

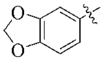
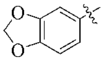
As can be observed, both electron-rich and electron-deficient arylstannanes reacted with **2** under the Stille conditions in good yields.[15]

Then, thiocyclobutenediones **3** and **5**−**7** were subjected to the Liebeskind−Srogl protocol with a variety of boronic acids to give nonsymmetric biarylcyclobutenediones[9] (Table 2).

The Liebeskind−Srogl reactions worked efficiently to give the corresponding products from moderate to excellent yields.

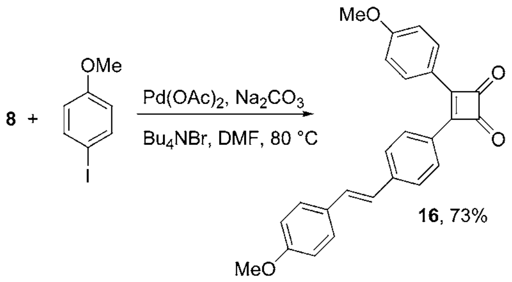
Table 2. Liebeskind−Srogl Cross-Coupling of **3** and **5**−**7**



entry	Ar₁	Ar₂	compd, % yield[a]
1	*p*-$CH_3OC_6H_4$-	*p*-CH_2=CHC_6H_4-	**8**, 74
2	*p*-$CH_3OC_6H_4$-	*p*-$Me_2NC_6H_4$-	**9**, 44
3	*p*-$CH_3C_6H_4$-	6-methoxy-2-naphthyl-	**10**, 50
4	*p*-$CH_3C_6H_4$-	3,4-dimethoxyphenyl-	**11**, 58
5	*p*-ClC_6H_4-	4-formylphenyl-	**12**, 76
6	*p*-ClC_6H_4-	4-bromophenyl-	**13**, 47
7		3-thienyl-	**14**, 56
8		2-furyl-	**15**, 90

[a] Isolated yields.

It tolerates a variety of functional groups that range from electron-releasing (entries 1−4) to electron-withdrawing (entries 5 and 6), including heterocyclic systems (entries 7 and 8).[16] The functional groups attached to the aryl systems allow further elaboration of the products. For instance, cyclobutenedione **8** was reacted with *p*-iodoanisole under the Heck conditions to yield **16** in 73% yield (eq 4).



(4)

16, 73%

In conclusion, we have prepared chlorothiocyclobutenedione **2** and demonstrated its utility in the efficient synthesis of nonsymmetrical bisarylcyclobutenediones. By using reaction conditions for the Stille coupling without CuI, organostannanes react exclusively at the Cl-bearing C atom. Then, by switching the reaction conditions to the Liebeskind−Srogl protocol in the presence of a stoichiometric amount of CuTC, the S-bearing C atom reacts with highly functionalized boronic acids. The nature of the different reaction centers of **2**, and the unique methods to activate them, makes this

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(12) Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc.* **1993**, 263.

(13) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.

(14) It has been reported in the literature that in cross-couplings or thioorganics with organostannanes the Cu(I) additive need not be a Cu(I) carboxylate. See ref 7e.

(15) **Typical experimental procedure**: In an oven-dried Schlenk tube, **2** (50.0 mg, 0.19 mmol) and *p*-methylphenyltributylstannane (95.0 mg, 0.23 mmol) were dissolved in anhyd. CH_3CN (3 mL) under N_2. Then, the mixture was purged with N_2 for 5 min whereupon $(CH_3CN)_2PdCl_2$ (2.5 mg, 0.009 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The mixture then was washed with hexanes (4 × 3 mL) to remove the tin byproducts, and the remaining CH_3CN phase was concentrated in vacuo. The final product (yellow solid, 17.2 mg, 58%) was purified by flash chromatography (SiO_2-gel, EtOAc/hexanes gradient).

(16) **Typical experimental procedure**: In an oven-dried Schlenk tube, **5** (50.0 mg, 0.16 mmol) and 6-methoxynaphthaleneboronic acid (81.0 mg, 0.4 mmol) were dissolved in dry THF (4 mL) under N_2. Then, the mixture was purged with N_2 for 5 min whereupon Pd_2bda_3 (1.47 mg, 0.001 mmol), TFP (1.1 mg, 0.004 mmol), and CuTC (91.8 mg, 0.48 mmol), were added. The reaction mixture was heated at 50 °C for 20 h, cooled to rt, and then quenched with satd. aq. NH_4Cl saturada. Then, it was extracted with EtOAc (3 × 10 mL), dried over $CaCl_2$, and filtered, and the volatiles were removed under reduced pressure. The product (yellow solid, 26.0 mg, 50%) was purified by flash chromatography (SiO_2-gel, EtOAc/hexanes gradient).

substrate amenable to other (both transition-metal-catalyzed and non-transition-metal-catalyzed) tandem processes that may be combined with the Liebeskind−Srogl reaction to yield more elaborate products. These studies and the anchoring of solid resins and fluorinated tags to the vinyl chloride moiety of **2** are underway in our laboratory and will be published in due course.

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Supporting Information Available: A complete description of all of the experimental procedures as well as the characterization of all of the compounds in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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