

Synthesis bis-thienyl-substituted cyclobutenedione *via* the Liebeskind-Srogl and Stille cross-coupling reactions

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to Professor Lanny S. Liebeskind on the occasion of his 70th birthday

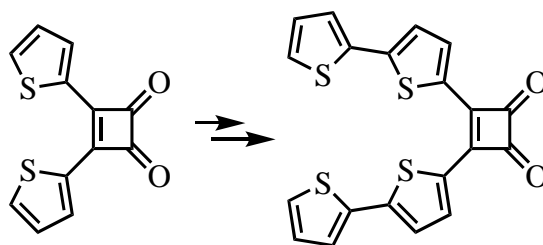
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Abstract

Dithien-2-yl and bis(dithien-2-yl)-substituted cyclobutenediones were prepared via Pd(0)-catalyzed cross-coupling reactions, namely, the Liebeskind-Srogl cross-coupling and Suzuki reactions in 85% and 82% yields, respectively.



Keywords: Thiophene, cyclobutenediones, Liebeskind-Srogl cross-coupling, palladium

Introduction

Oligothiophenes are among the most prominent π -conjugated organic oligomers. Their uses span molecular nanowires,¹ organic dyes for molecular photovoltaics,^{2,3} organic field-effect transistors (OFET),⁴ and in general in molecular electronics.⁵⁻⁸ Thiophenes are remarkable heterocycles which are endowed with very useful properties such as efficient charge transport, tunable redox potentials, and high polarizability.⁹⁻¹¹ Donor-acceptor (D-A) systems that contain thiophene units have become important over the last few years chiefly because of their useful properties.⁹⁻¹¹ Herein, we present our efforts toward the synthesis of a novel derivative possessing a D-A architecture.

The design of bis(dithienyl)cyclobutenedione **1** was based upon two premises, i.e., (a) charge-separation is ensured by capping the thiophene chains with a cyclobutenedione (an electron-withdrawing fragment) and (b) if desired, cyclobutenedione could be transformed into either a quinone or a hydroquinone thereby changing the electronic and geometric features of **1** (Figure 1).¹²⁻¹⁵

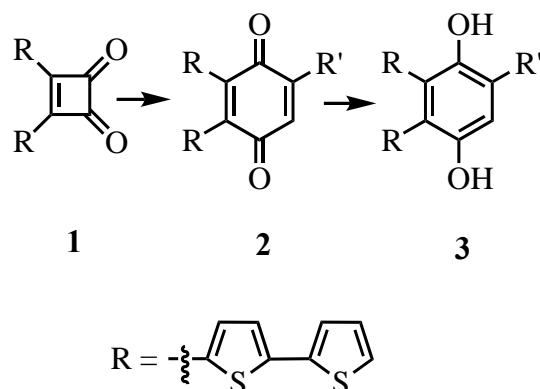
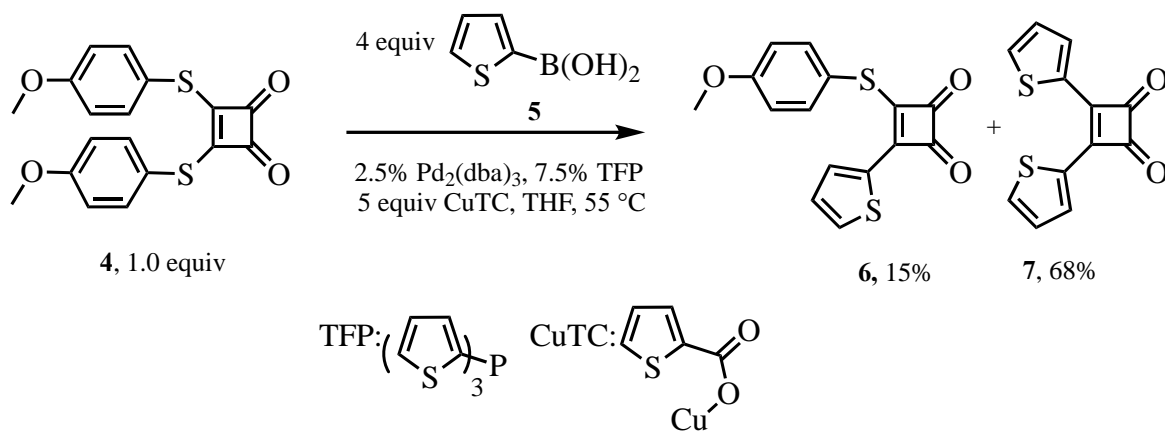


Figure 1. Possible transformation of the cyclobutenedione nucleus.

Being aware of the importance of the cyclobutenedione synthetic transformations, over the last few years our research group has devoted a significant amount of effort to develop a methodology that would allow for the introduction of different aryl and heteroaryl substituents at the olefinic positions.¹⁶⁻¹⁷ In this contribution, we disclose the application of that methodology to achieve the synthesis of the thien-2-yl-cyclobutenedione derivatives.

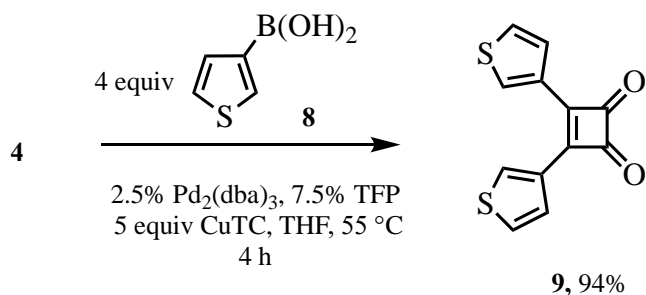
Results and Discussion

Our initial efforts to prepare **7** focused on our recently developed cross-coupling of 3,4-bis-(4-methoxyphenylthio)cyclobutenedione **4** with organoboron reagents to yield symmetric disubstituted cyclobutenediones.¹⁸ However, when this protocol was applied to the target molecule under a number of different reaction conditions, we always obtained a mixture of **4** and the mono- and bis-substituted products **6** (15% yield) and **7** (68% yield) (Scheme 1).



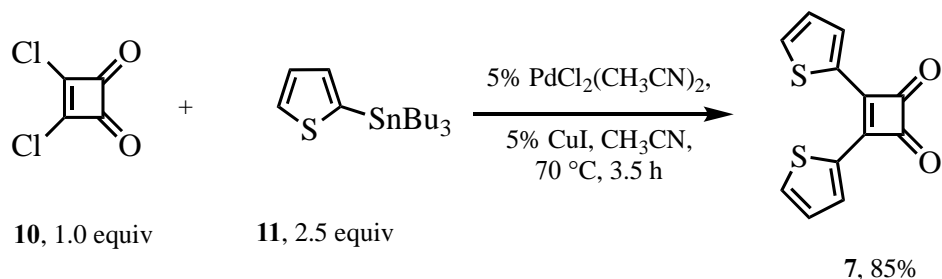
Scheme 1

These results are in contrast to those observed with 3-thienylboronic acid **8**, whereby under similar reaction conditions, isomer **9** was obtained in 94% yield (Scheme 2).



Scheme 2

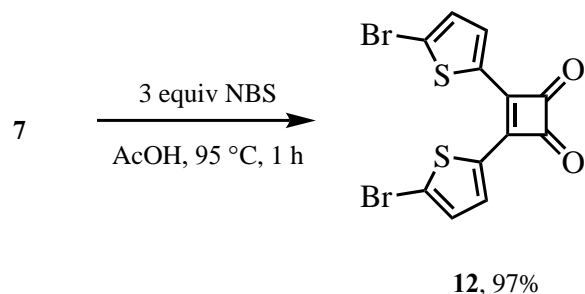
In view of these results, we decided to change our approach. The Suzuki cross-coupling between 2-thienylboronic acid **5** and 3,4-dichloro-3-cyclobuten-1,2-dione¹⁹ **10** ($\text{Pd}(\text{OAc})_2$, S-Phos, K_3PO_4 in toluene or THF) gave only traces of **7**. Finally, **7** was efficiently prepared in 85% by using the Stille cross-coupling reaction²⁰ between 3,4-dichloro-3-cyclobuten-1,2-dione **10** and commercially available tributyl(2-thienyl)stannane **11** (Scheme 3).



Scheme 3

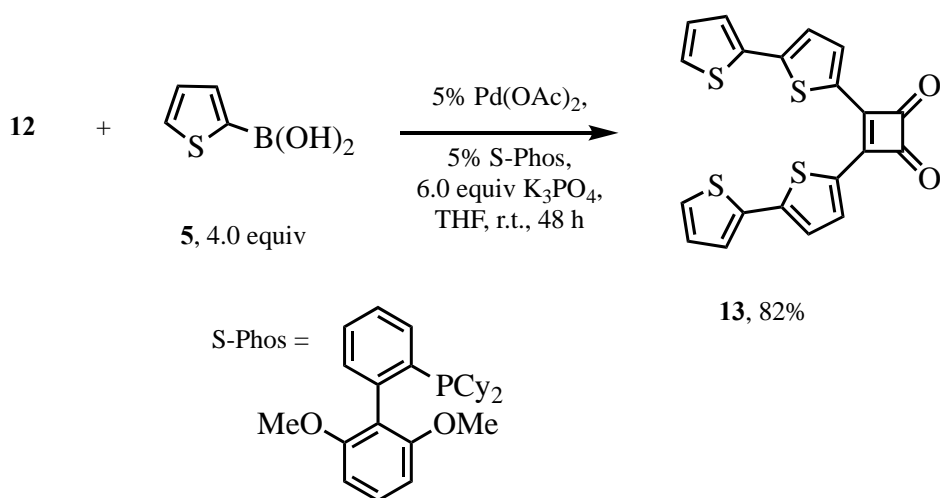
In order to incorporate the remaining thiophene units to **7** via a transition metal-catalyzed reaction, bromination of **7** was attempted with Br_2 in AcOH. However, even at 120 °C, no reaction was observed,

presumably, due to the deactivating effect of the electron-withdrawing cyclobutenedione unit. On the other hand, treatment of **7** with three equivalents of NBS in AcOH gave the desired product **12** in excellent yield (Scheme 4).



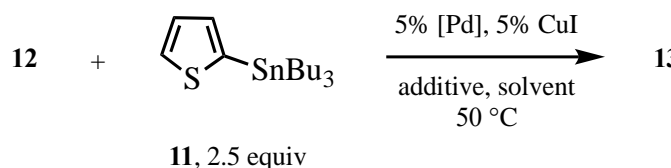
Scheme 4

With dibromide **12** in hand, we proceeded to react it with 2-thienylboronic acid according to the Suzuki conditions reported by Buchwald²⁰ (Scheme 5).



Scheme 5

Despite the excellent results obtained using the Suzuki coupling to prepare **13**, when the reaction was repeated at a larger scale, it became very sluggish with a significant amount of **12** remaining even after 3 days. We then turned our attention to the Stille coupling²¹⁻²² and carried out an optimization study for the synthesis of **13** (Table 1).

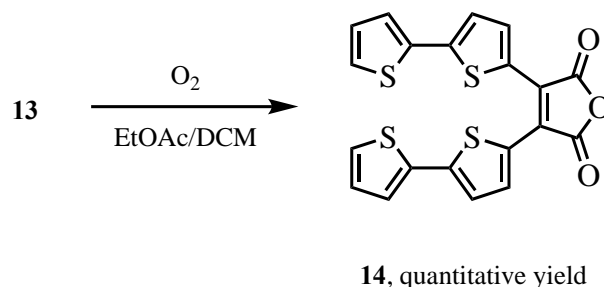
Table 1. Optimization of the Stille Reaction for the Synthesis of **13**


entr y	[Pd]	solven t	additiv e	Time (h)	% yield 13 ^a
1	PdCl ₂ (CH ₃ CN)) ₂	CH ₃ C N	-	72	nr
2	PdCl ₂ (PPh ₃) ₂	THF	-	2	75
3	PdCl ₂ (PPh ₃) ₂	DMF	-	1.5	84
4	PdCl ₂ (PPh ₃) ₂	THF	4.0 CsF	2	77
5	PdCl ₂ (PPh ₃) ₂	DMF	4.0 CsF	10 min	80

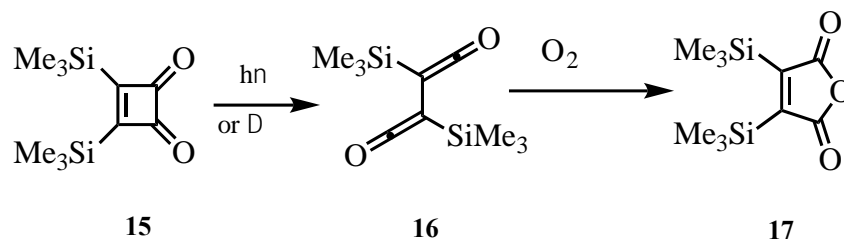
^a isolated yields.

The beneficial effect that fluoride has in the Stille reaction²³ was observed in this system as well, for **13** was isolated in 80% yield after only 10 min.

During the isolation and characterization of **13** we made an interesting observation. Once in solution (hexanes/EtOAc) and exposed to air, [**13** remained unchanged if the solution remained under N₂] the originally orange solution of **13** gradually turned deep red. TLC of this solution showed that **13** slowly transformed into a different compound. ¹H NMR of the new compound was not very informative since it displayed the same signals as **13**, only slightly shifted. However, ¹³C NMR of this material showed no carbonyl signal in the region typical of cyclobutenediones (190-200 ppm), it did, however, show a signal of a carbonyl group at 164.6 ppm, which is typical of anhydride carbonyl groups (C=O signal of maleic anhydride appears at 164.5 ppm). Based upon this information, it is believed that oxygen inserted between the carbonyl groups of **13** (Scheme 6).

**Scheme 6**

In addition to the spectral data described above, HRMS analysis gives a molecular peak that matches the structure proposed. This oxidation reaction is not unprecedented. Tidwell and Zhao²⁴ showed that bisketene **16**, generated either thermally or photochemically from its corresponding cyclobutenedione precursor, formed the substituted maleic anhydride on exposure to oxygen (Scheme 7).



Scheme 7. Insertion of oxygen into cyclobutenediones.

A similar process may be operating in the transformation depicted in eq 6. It is important to notice that this process takes place only after two more thiophene units have been incorporated to **7**. This seems to indicate that extension of the conjugated system activates the cyclobutenedione ring toward oxygen insertion.

Conclusions

An efficient methodology to prepare a D-A system comprising two bis-thienyl groups attached to a cyclobutenedione has been developed. Both the Liebeskind-Srogl and Stille cross-coupling reactions were attempted to furnish the target molecule, the latter being the method that gave the best results. The addition of CsF to the key Stille reaction was crucial to the success of the synthesis of **13**. When **13** was exposed to air, the corresponding anhydride **17** was smoothly formed by the insertion of oxygen between the carbonyl groups. This transformation is currently under study in our laboratory and the results will be reported in due course.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform (CDCl_3), with either tetramethylsilane (TMS) (0.00 ppm ^1H , 0.00 ppm ^{13}C), chloroform (7.26 ppm ^1H , 77.00 ppm ^{13}C). Data are reported in the following order: chemical shift in ppm, multiplicities (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), exch (exchangeable), app (apparent)), coupling constants, J (Hz), and integration. Infrared spectra were recorded on a FTIR spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67–100 %), m (medium, 40–67%), and w (weak, 20–40%). Melting points are not corrected. TLC was conducted in silica gel on Al foils. Detection was by UV light (254 or 365 nm). HRMS samples were ionized by ESI+ and recorded via the TOF method.

Synthesis of 3,4-Bis(thien-2-yl)-3-cyclobuten-1,2-dione **7 using the Liebeskind-Srogl cross-coupling.** A 50 mL Schlenk flask under N_2 was charged with **4** (100 mg, 0.28 mmol, 1.0 equiv), thienylboronic acid **5** (142.8 mg, 1.1 mmol, 4.0 equiv), and anhyd THF (10 mL), and the resulting yellow solution was deoxygenated by bubbling N_2 for 5 min. Then, CuTC (266 mg, 1.4 mmol, 5.0 equiv), $\text{Pd}_2(\text{dba})_3$ (6.4 mg, 2.5×10^{-3} mmol), and trifurylphosphine (4.9 mg, 7.5×10^{-3} mmol) were added. The reaction mixture was heated at 55 °C for 22 h, the heating bath was removed, and the volatiles were removed in vacuo. The crude material was purified by flash chromatography (SiO_2 gel, 5% ethyl acetate/hexanes gradient) to give the product as a yellow solid (46.7 mg, 68%). Recrystallization was carried out by using DCM/cold petroleum ether. Mp 200-201 °C; TLC (SiO_2 ,

20% EtOAc/hexanes, $R_f = 0.4$); IR (KBr, cm^{-1}): 3108.4 (w), 3085 (d), 1764 (s), 1567 (s), 1417 (m), 1405 (m); ^1H NMR (500 MHz, CDCl_3): δ 8.43 (dd, J 3.8, 0.9 Hz, 2H), 7.96 (dd, J 5.0, 0.9 Hz, 2H), 7.39 (dd, J 4.9, 3.9 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.0, 173.2, 135.2, 134.0, 129.3, 129.3; HRMS ($\text{C}_{12}\text{H}_7\text{O}_2\text{S}_2$, $\text{M}+1\text{H}$) calcd. 246.9882, found 246.9883. Along with **7**, the mono-coupled product **6** was isolated (13.0 mg, 15%) as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, J 3.4 Hz, 1H), 7.91 (d, J 5.0 Hz, 1H), 7.56 (d, J 8.7 Hz, 2H), 7.35 – 7.33 (t, 1H), 6.97 (d, J 8.7 Hz, 2H), 3.86 (s, 3H).

Synthesis of 3,4-Bis(thien-2-yl)-3-cyclobuten-1,2-dione 7 using the Stille cross-coupling. A 100 mL two-neck round bottom flask was charged with thien-2-yl stannane **6** (1.6 g, 4.29 mmol, 2.5 equiv), CH_3CN (16 mL), and a stir bar under N_2 . The reaction mixture was purged with N_2 during 5 min after which dichlorocyclobutenedione **3** (261.7 mg, 1.73 mmol, 1 equiv), $\text{PdCl}_2[\text{CH}_3\text{CN}]_2$ (22.2 mg, 0.09 mmol, 5 mol%) and CuI (16.6 mg, 0.09 mmol, 5 mol%) were added. The reaction mixture was heated at 70 °C for 3.5 h then it was allowed to reach rt. Once the reaction mixture reached rt, an abundant yellow precipitate formed. The acetonitrile volume was doubled, and the solid dissolved completely. The acetonitrile layer was extracted with hexanes (3 x 15 mL) to eliminate the tin by-products, then the solvent was evaporated under reduced pressure. The final product was purified by flash chromatography (SiO_2 -gel) using an AcOEt/hexanes gradient. The resulting solid was washed with hexanes (3 x 15 mL) and dried under vacuum. The product (359.7 mg, 1.46 mmol, 85%) was obtained as yellow crystalline solid. Mp 200-201 °C.

Synthesis of 3,4-Bis(5-bromothien-2-yl)cyclobut-3-ene-1,2-dione 12. A 50 mL Schlenk tube under N_2 was charged with **7** (20 mg, 0.0812 mmol, 1.0 equiv.), *N*-bromosuccinimide (43.36 mg, 0.2436 mmol, 3.0 equiv.), glacial acetic acid (3.0 mL). The reaction mixture was stirred at rt for 5 min, then heated at reflux at 95 °C for 1 h, after which it was allowed to reach rt. An abundant yellow solid was observed. A saturated aq NH_4Cl solution was added (4 mL) followed by 0.25M NaOH (4 mL) and stirring continued for 10 min. The yellow solid was filtered using a Whatmann filter paper and washed with 0.1M NaOH (4 x 5 mL) and then with H_2O (2 x 5 mL). The yellow solid was dried under vacuum (31.6 mg, 97% yield). Recrystallization was carried out using DCM/cold petroleum ether. Mp 192-193 °C; TLC (30% EtOAc/Hexanes, $R_f = 0.7$); IR (KBr, cm^{-1}): 3095 (w), 1786 (s), 1761 (s), 1584 (m), 1411 (m); ^1H NMR (500 MHz, CDCl_3) δ 8.13 (d, J 3.8, 2H), 7.35 (d, J 3.9, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 192.2, 171.2, 134.4, 132.5, 130.7, 124.9; HRMS ($\text{C}_{12}\text{H}_5\text{Br}_2\text{O}_2\text{S}_2$, $\text{M}+1\text{H}$) calcd. 404.8100, found 404.8071.

Synthesis of 3,4-bis([2,2'-bithien]-5-yl)cyclobut-3-ene-1,2-dione 13. A 25 mL Schlenk tube under N_2 was charged with **12** (20 mg, 0.0498 mmol, 1.0 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (1.74 mg, 0.0025 mmol, 5 mol%), CuI (0.47 mg, 0.0025 mmol, 5 mol%), CsF (30.24 mg, 0.1991 mmol, 4.0 equiv), DMF (4 mL). The reaction was stirred at rt for 1 min after which 2-(tributylstannyl)thiophene **11** was added (47 mg, 0.1244 mmol, 2.5 equiv). The reaction mixture was stirred at 50 °C for 10 min. After 10 min., the reaction was allowed to reach rt and quenched by adding Et_2O (15 mL) and equal volume of H_2O . The aqueous layer was extracted with Et_2O (5 x 15 mL) and the organic layers were combined and dried over MgSO_4 . The mixture was filtered through a cotton plug and concentrated under reduced pressure to get a red colored oily material. After trituration with hexanes, a red solid formed, which was washed further with hexanes (10 x 5 mL) to remove tin impurities. Finally, the material was washed with 2.5% EtOAc/hexanes (5 mL) to give the final product (16.4 mg, 80%). Mp > 196 °C (dec); TLC (30% EtOAc/Hexane, $R_f = 0.5$); IR (KBr, cm^{-1}): 3098 (w), 1756 (s), 1572 (m), 1438 (s); ^1H NMR (500 MHz, CDCl_3) δ 8.33 (d, J 4.1 Hz, 2H), 7.46 (dd, J 3.6, 0.9 Hz, 2H), 7.44 – 7.41 (m, 4H), 7.13 (dd, J 5.1, 3.7 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 192.8, 171.2, 147.6, 136.0, 135.1, 128.7, 127.7, 127.6, 126.5, 125.7; HRMS ($\text{C}_{20}\text{H}_{11}\text{O}_2\text{S}_4$, $\text{M}+1\text{H}$) calcd 410.9636, found 410.9639.

Synthesis of 2,3-bis(5-[2,2']-bithien-5-yl) maleic anhydride 14. Compound **13** (49 mg, 0.1192 mmol) was dissolved in a 1 :1 AcOEt:DCM mixture (20 mL) in a beaker. The reaction mixture was stirred at rt under air for 5 days, solvent was replenished when necessary to avoid dryness. After evaporation of the solvent the dark red colored compound **14** was obtained (50.9 mg, 100%). M.p.= 186-187 °C. TLC (30% EtOAc/Hexane, R_f = 0.54); IR (KBr, cm^{-1}): 3108 (d), 1745 (s), 1439 (s); ^1H NMR (500 MHz, CDCl_3) δ 7.99 (d, J 4.1 Hz, 2H), 7.34 (dd, J 6.7, 4.4 Hz, 4H), 7.25 (d, J 4.1 Hz, 2H), 7.08 (dd, J 5.0, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.4, 144.6, 136.0, 134.0, 128.4, 127.3, 126.7, 126.7, 125.7, 124.4; HRMS ($\text{C}_{20}\text{H}_{11}\text{O}_3\text{S}_4$, $\text{M}+1\text{H}$) calcd 426.9600, found 426.9586.

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Supplementary Material

^1H , ^{13}C spectra of the compounds prepared are available as supplementary material.

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