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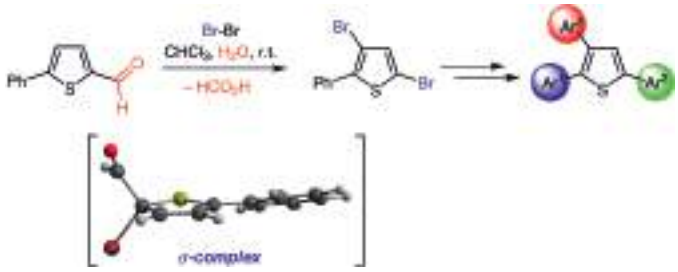
Decarbonylative Dibromination of 5-Phenylthiophene-2-carbaldehyde with Bromine

Vladimir Ajdačić[a]
Stepan Stepanović[b]
Mario Zlatović[a]
Maja Gruden[a]
Igor M. Opsenica*[a]

[a] Faculty of Chemistry, University of Belgrade, PO Box 51, Studentski trg 16, 11158 Belgrade, Serbia
igorop@chem.bg.ac.rs
[b] Institute of Chemistry Technology and Metallurgy, University of Belgrade, Studentski trg 16, 11158 Belgrade, Serbia



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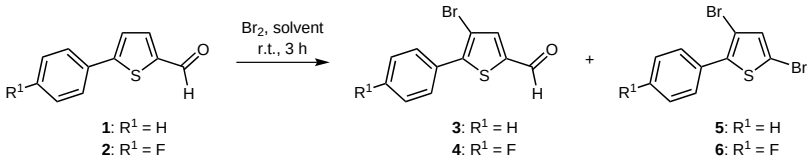
Abstract The decarbonylative dibromination of 2-thiophenecarboxaldehyde derivatives with bromine under mild conditions is developed. The mechanism for the decarbonylation is investigated by experimental and instrumental techniques and is extended by a computational study. Alongside removal of the formyl group, this method enables functionalization of the starting compounds in a single reaction step, which can be further exploited for the synthesis of 2,5-diaryl-3-bromothiophenes and 2,3,5-triarylthiophenes.

Key words deformylation, thiophene, reaction mechanism, Wheland intermediate, Suzuki–Miyaura reaction

The various methods for removing a formyl group from a range of organic molecules represent essential protocols in organic synthesis and in biology as well. In Nature, cytochrome P450 enzymes are the major enzymes involved in deformylation reactions.[1] Over the past few decades, the metal-mediated decarbonylation of aldehydes has been extensively investigated.[2] Decarbonylation reactions mediated by a stoichiometric amount of Wilkinson's catalyst have been the most frequently employed.[3] Significant progress toward a catalytic decarbonylation of aldehydes was achieved with more reactive cationic Rh complexes.[4] The catalytic decarbonylation of aldehydes under mild reaction conditions has been developed by employing various metal-based systems, including those with Pd/C[5] or $Pd(OAc)_2$ as a precatalyst,[6] and Ir[7] or Ru complexes.[8] There are several efficient metal-free decarbonylation methods available employing aliphatic tertiary or secondary amines,[9] molecular O_2,[10] di-*tert*-butyl peroxide,[11] I_2/DMSO,[12] and $BF_3{\cdot}Et_2O$[13] as reagents. Very recently, the decarbonylation of an aromatic aldehyde in the presence of bromine was observed.[14]

Herein, we report the deformylation and dibromination of 2-thiophenecarboxaldehyde derivatives using bromine under mild conditions. To the best of our knowledge, this is the first report of this kind of transformation on an aromatic heterocyclic system.

During the synthesis of 4-bromo-5-phenylthiophene-2-carbaldehyde (**3**), we have observed deformylation and dibromination of the starting compound in the presence of bromine in commercially available chloroform (puriss p.a., 99.0–99.4%) at room temperature (Scheme 1). 4-Bromo-5-phenylthiophene-2-carbaldehyde (**3**) was obtained as the major product while dibromide **5** was isolated as a side product of the reaction (Table 1, entry 1). Aldehyde **2**, with a *para*-fluoro substituent on the phenyl ring, reacted in the similar manner. The brominated aldehyde **4** was isolated as the major product, while deformylation–dibromination product **6** was obtained as the minor compound (Scheme 1 and Table 1, entry 6). In order to gain mechanistic insight into this transformation, we have performed the same reactions in $CDCl_3$ and analyzed the spectroscopic data of the reaction mixture. To our surprise, compounds **3** and **4** were identified as the only products of the respective reactions. This finding led us to conclude that there was an additional component of the reaction mixture that was involved in the deformylation pathway besides bromine. Thus, we performed the same reactions in dry chloroform (distilled over P_2O_5), and aldehydes **3** and **4** were isolated as the principal products, accompanied by trace amounts of **5** and **6**, respectively (Table 1, entries 2 and 7). Upon addition of water to the reaction mixture the yields of the dibromides **5** and **6** increased dramatically (Table 1, entries 3 and 8). The results of these experiments indicated that the presence of water was critical to the success of the deformylation.



Scheme 1 The decarbonylative dibromination reaction

Table 1 Optimization of the Reaction Conditions

Entry	Substrate	Br_2 (equiv)	Solvent	Yields (%)[a]		
				1	**3**	**5**
1	**1**	1.2	$CHCl_3$[b]	0	67	25
2	**1**	1.6	dry $CHCl_3$[c]	0	75	2
3	**1**	1.6	$CHCl_3/H_2O$ (12:1, v/v)	0	52	36
4	**1**	3	AcOH	0	57	28
5	**1**	3	CD_3CO_2D	0[d]	85[d]	15[d]
				2	**4**	**6**
6	**2**	1.2	$CHCl_3$[b]	0	71	28
7	**2**	1.6	dry $CHCl_3$[c]	0	86	9
8	**2**	1.6	$CHCl_3/H_2O$ (12:1, v/v)	0	38	53

[a] Yield of isolated product.
[b] Puriss p.a., 99.0–99.4%.
[c] Distilled over P_2O_5.
[d] Yield (%) determined by ^1H NMR spectroscopy.

Notably, the decarbonylative dibromination also occurred in acetic acid (Table 1, entry 4). To gain insight into the possible mechanism of the decarbonylative dibromination reaction sequence we performed the reaction in CD_3CO_2D and analyzed the spectroscopic data of the reaction mixture (Table 1, entry 5 and Figure 1).

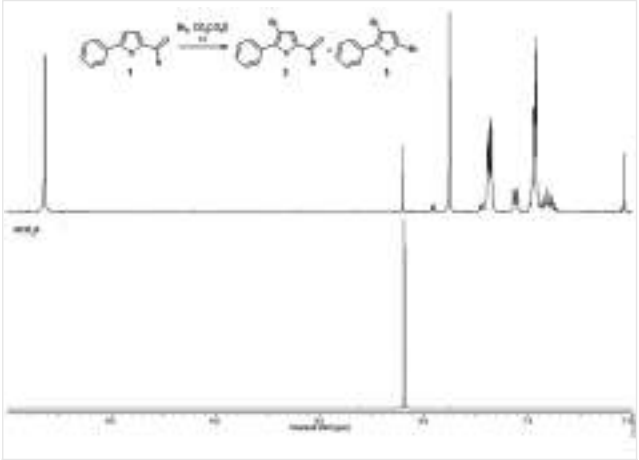
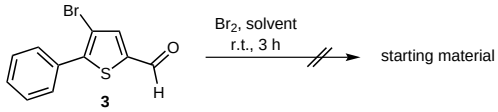


Figure 1 ^1H NMR spectroscopic analysis of the reaction mixture in CD_3CO_2D

Based on the spectroscopic analysis, it was concluded that during deformylation, formic acid is liberated from the reaction mixture. The amount of released formic acid equals exactly the amount of dibromide **5** (see the Supporting Information).

It is very important to note that compound **3** was not transformed into **5** in the presence of bromine (Scheme 2), which indicated that the transformation of starting aldehyde **1** into compounds **3** and **5** most likely proceeds via two distinct reaction pathways.



Scheme 2 Reaction of **3** with bromine

In order to rationalize the intriguing outcome of the decarbonylative dibromination, and to account for the product ratio, DFT calculations were performed for the proposed reaction pathways. Since the rate-limiting step of the aromatic substitution reaction is the formation of the σ-complex, that is accompanied by the loss of the aromatic stabilization, we located the transition states (***TS1*** and ***TS2***) and subsequent intermediates (***σ-complex-1*** and ***σ-complex-2***), formed in this phase of the reaction pathway (Figure 2). It is a well-known fact that hybrid density functional approximations (DFAs) perform superior for the reaction energetics.[15] Thus, the most commonly utilized hybrid DFA, B3LYP, with Grimme's third-generation dispersion energy correction, was chosen as the most suitable level of theory. The results are presented schematically in Figure 2. The left side of the reaction landscape (depicted in red color) leads to the 'normal' aromatic substitution, and proceeds via the transition state ***TS1*** and the formation of intermediate ***σ-complex-1***. The final step, not the rate-limiting step, represents the elimination of H^+ and the recovery of aromatic stabilization.

As outlined in the right side of Figure 2 (depicted in blue color), the alternative mechanistic possibility, the attack of bromine on the carbon next to the formyl group, proceeds via transition state ***TS2*** and the formation of intermediate ***σ-complex-2***, but depends subsequently on the facility of decarbonylation in order to obtain the corresponding aromatic compound halogenated at that position.

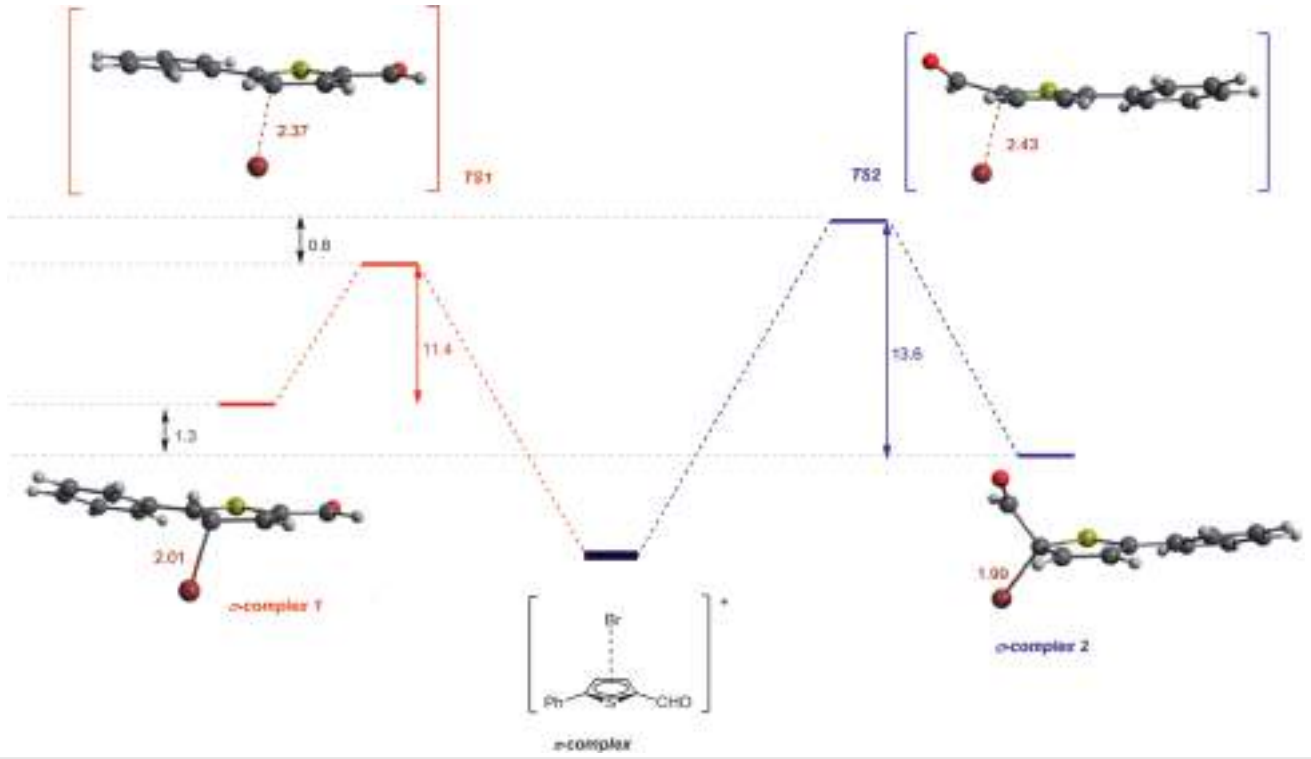
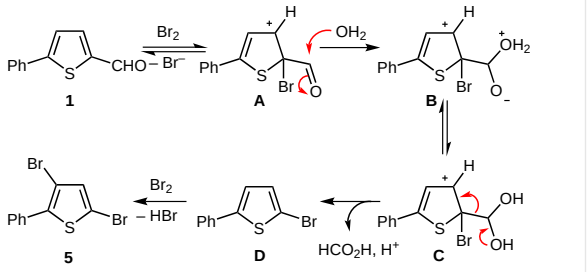


Figure 2 Calculated geometries and transition states for the formation of a σ-complex (rate-limiting step) during the aromatic halogenation of 5-phenylthiophene-2-carbaldehyde (**1**). Gibbs free energies (in kcal/mol), obtained using the B3LYP/TZP level of theory, are given relative to the lower pathway

Our results presented in Figure 2 show that the barriers for the two possible mechanistic pathways are almost identical (***TS1*** is lower only by 0.8 kcal/mol). Therefore, if ***σ-complex-2*** can easily eliminate the formyl group, both products should be obtained in equal amounts. This corroborates the experimental observation that both products are obtained in 52:36 ratio in the presence of water. Contrary to this, in the absence of water, ***σ-complex-2*** cannot proceed toward the deformylated product, and the barrier height for the reversible process, elimination of bromine and formation of a ***π-complex***, is sufficiently low to explain the dominant formation of compound **3**.

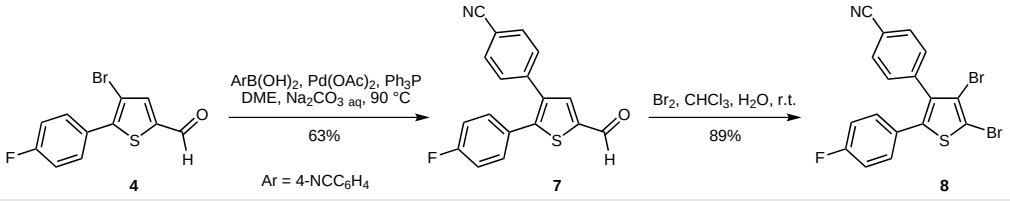
On the basis of the above results, we propose the mechanism shown in Scheme 3.



Scheme 3 Proposed reaction mechanism

The cationic reaction intermediate, arenium ion **A**, known as a σ-complex or Wheland intermediate, is formed in the rate-determining step. Addition of water to the C=O π-bond occurs to give a tetrahedral intermediate. After breakdown of the tetrahedral intermediate through aromatization, bromide **D** and formic acid are liberated. The subsequent bromination of **D** affords dibromide **5**.

The influence of different electron-withdrawing groups on the phenyl ring with respect to the scope of the decarbonylative dibromination reaction was also studied. Under the given reaction conditions, aldehydes bearing a nitro or cyano group at the *para* position yielded a complex reaction mixture, with the starting compounds as the predominant components (see the Supporting Information). Apparently, the nitro and cyano group reduce the electron density from the π system of the phenyl and thiophene rings, thereby making the rings less reactive toward an electrophile. On the other hand, aldehyde **7**, prepared by Suzuki–Miyaura reaction starting from compound **4**, was successfully transformed into dibromide **8** in high yield using the decarbonylative dibromination sequence (Scheme 4). Evidently the decarbonylative dibromination reaction is substrate-dependent.



Scheme 4 Synthesis of 4-[4,5-dibromo-2-(4-fluorophenyl)thiophen-3-yl]benzonitrile (**8**)

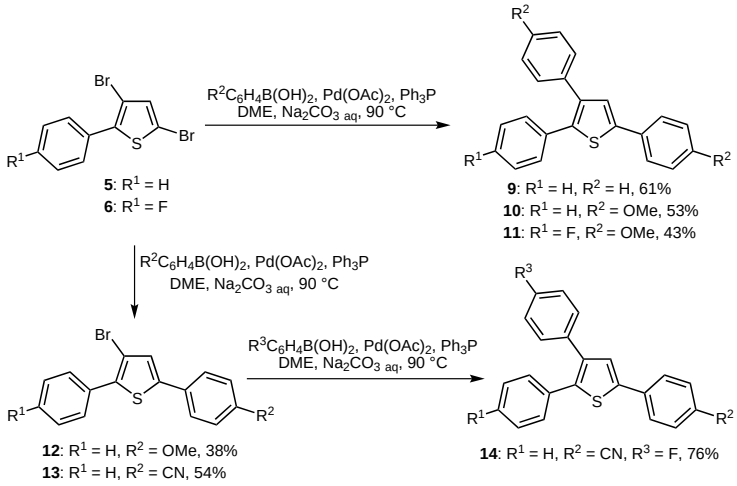
Aryl-substituted thiophenes are of great importance in medicinal chemistry[16] as well as in materials science.[17] Therefore, much effort has been devoted to the development of synthetic procedures for the synthesis of this class of compounds. The Suzuki–Miyaura cross-coupling reaction is one of the most powerful methods for the preparation of polyarylated thiophenes.[18]

In continuation of this study, several 2,5-diaryl-3-bromothiophenes and 2,3,5-triarylthiophenes were prepared by Suzuki–Miyaura reaction starting from dibromides **5** and **6** (Scheme 5). Dibromides **5** and **6** were successfully coupled with a series of arylboronic acids under Suzuki–Miyaura cross-coupling reaction conditions affording compounds **9**–**14** in moderate to good yields.[19] Based upon literature precedent,[18] the regioselectivity in the cross-coupling reaction is as expected. To the best of our knowledge, this is the first time that 3,5-dibromo-2-arylthiophenes have been used for the synthesis of differently substituted 2,3,5-triarylthiophenes.

Finally, we compared the NMR spectra of synthesized compounds **9**[20] and **10**[16b] with the literature data, and comparable spectroscopic data were used as the final proof for the structure of their precursor, dibromide **5**. Interestingly, the Suzuki–Miyaura cross-coupling reaction of dibromide **8** with different arylboronic acids did not proceed.

In conclusion, an unexpected decarbonylative dibromination reaction of 5-phenylthiophene-2-carbaldehyde and its mechanism has been investigated by experimental and instrumental techniques, and extended by a computational study of the proposed reaction pathways. The decarbonylative dibromination of 2-thiophenecarboxaldehyde derivatives occurs under mild reaction conditions with bromine in a mixture of $CHCl_3/H_2O$ at room temperature. The investigation of the reaction mechanism indicated that formic acid was liberated from the reaction mixture during deformylation. This serendipitous deformylative dibromination is not a general synthetic method, our goal was rather to enlighten and offer thorough explanation for the mechanism of this unusual synthetic path that we have noticed. In addition, it was shown that this reaction followed by a Suzuki–Miyaura cross-coupling reaction can be used for the synthesis of 2,5-diaryl-3-bromothiophenes and 2,3,5-triarylthiophenes. Further studies on the scope and synthetic applications of the decarbonylative dibromination reaction of other heteroaromatic aldehydes are in progress.

Dry-flash chromatography was performed on SiO_2 (0.018–0.032 mm). Melting points were determined on a Boetius PMHK apparatus and were not corrected. IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. ^1H and ^{13}C NMR



Scheme 5 Synthesis of 2,5-diaryl-3-bromothiophenes and 2,3,5-triarylthiophenes

spectra were recorded on a Bruker Ultrashield Avance III spectrometer (at 500 and 125 MHz, respectively) using tetramethylsilane (TMS) as the internal standard. The NMR solvents are specified individually for each compound. Chemical shifts are expressed in parts per million (ppm) on the (δ) scale. Chemical shifts were calibrated relative to those of the solvent. ESI MS spectra of the synthesized compounds were recorded on an Agilent Technologies 6210 Time-of-Flight LC–MS instrument in positive ion mode using MeOH/H_2O = 1:1 with 0.2% HCOOH as the carrying solvent solution. The samples were dissolved in pure MeOH (HPLC grade). The selected values are as follows: capillary voltage = 4 kV; gas temperature = 350 °C; drying gas = N_2, 12 L·min^{-1}; nebulizer pressure = 45 psig; fragmentator voltage = 70–200 V. After extensive optimizations that included the utilization of different instruments and ionization sources, we were unable to obtain HRMS for compounds **5**, **6**, **8** and **12**. The samples were analyzed on LC/ESI MS 6210 Time-of-Flight (Agilent Technologies) and Orbitrap XL (Thermo Fisher Scientific) instruments. For ionization, we tried ESI, APCI and APPI sources in both positive and negative mode. We also added some extra Na^+ to the eluent in order to obtain $[M + Na]^+$ ionization, but this did not work. All the yields reported refer to isolated yields. GC–MS spectra of the synthesized compounds were acquired on an Agilent Technologies 7890A apparatus equipped with a DB-5 MS column (30 m × 0.25 mm × 0.25 µm), a 5975C MSD and FID detector. The selected values are as follows: carrier gas was He (1.0 mL/min), temperature linearly increased from 40–315 °C (10 °C/min), injection volume = 1 µL, temperature = 250 °C, temperature (FID detector) = 300 °C, and EI mass spectra range: *m*/*z* 40–550.

Decarbonylation–Dibromination in $CHCl_3/H_2O$; Typical Procedure

To a solution of aldehyde **1** (76 mg, 0.40 mmol) in $CHCl_3$ (700 µL) and H_2O (70 µL) was added a solution of bromine (33 µL, 0.64 mmol) in $CHCl_3$ (330 µL). The resulting solution was stirred at r.t. for 3 h. To the reaction mixture was added sat. $Na_2S_2O_3$ solution and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with sat. $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to yield **3** (56 mg, 52%) as a yellow solid and **5** (46 mg, 36%) as a colorless oil.

4-Bromo-5-phenylthiophene-2-carbaldehyde (3)[21]

Mp 57–60 °C.

IR (ATR): 3310, 3082, 3053, 3026, 2845, 1678, 1645, 1519, 1449, 1430, 1394, 1309, 1226, 1122, 1031, 997, 966, 915, 842, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.72 (s, 1 H), 7.70–7.67 (m, 2 H), 7.50–7.45 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.8, 148.1, 141.3, 139.8, 131.8, 129.7, 129.0, 128.8, 108.8.

GC–MS: *m*/*z* = 267.9 $[M]^+$ (^{81}Br).

3,5-Dibromo-2-phenylthiophene (5)

Colorless oil.

IR (ATR): 3096, 3057, 3023, 2953, 2923, 2852, 1597, 1527, 1504, 1486, 1445, 1300, 1130, 982, 819, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.55 (m, 2 H), 7.47–7.36 (m, 3 H), 7.02 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.0, 133.6, 132.0, 128.9, 128.6, 111.6, 106.7.

GC–MS: *m*/*z* = 317.8 $[M]^+$.

4-Bromo-5-(4-fluorophenyl)thiophene-2-carbaldehyde (4) and 3,5-Dibromo-2-(4-fluorophenyl)thiophene (6)

Following the typical procedure, **4** was obtained as a yellow solid (9.5 mg, 38%) and **6** as a colorless solid (15.5 mg, 53%).

Compound 4

Mp 105–110 °C.

IR (ATR): 3306, 3092, 2923, 2848, 2815, 1894, 1677, 1599, 1524, 1441, 1404, 1313, 1296, 1229, 1158, 1123, 1096, 1013, 971, 847, 824 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.72 (s, 1 H), 7.69–7.64 (m, 2 H), 7.20–7.14 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.7, 163.4 (d, *J* = 249.1 Hz), 146.8, 141.4, 139.7, 131.0 (d, *J* = 8.1 Hz), 127.9 (d, *J* = 2.8 Hz), 116.0 (d, *J* = 21.6 Hz), 108.9.

GC–MS: *m*/*z* = 284.9 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_7BrFOS$: 284.93795; found: 284.93698.

Compound 6

Mp 83–84 °C.

IR (ATR): 3194, 3117, 3063, 2921, 2852, 1886, 1735, 1652, 1599, 1535, 1492, 1443, 1403, 1301, 1233, 1153, 1135, 1093, 1012, 980, 953, 836, 804 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 2 H), 7.15–7.09 (m, 2 H), 7.02 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 248.2 Hz), 138.8, 133.6, 130.8 (d, *J* = 8.1 Hz), 128.1 (d, *J* = 2.6 Hz), 115.7 (d, *J* = 21.6 Hz), 111.6, 106.9.

GC–MS: *m*/*z* = 335.8 $[M]^+$.

4-[2-(4-Fluorophenyl)-5-formylthiophen-3-yl]benzonitrile (7)

To a dry glass flask purged with argon were added $Pd(OAc)_2$ (4.3 mg, 0.019 mmol), Ph_3P (20 mg, 0.077 mmol) and dry DME (3 mL). The resulting solution was stirred at r.t. for 10 min, and 4-bromo-5-(4-fluorophenyl)thiophene-2-carbaldehyde (**4**) (110 mg, 0.386 mmol) and Na_2CO_3 (aq) (2 M, 0.65 mL, 1.3 mmol) were added. After 5 min, a solution of 4-cyanophenylboronic acid (56.7 mg, 0.386 mmol) was added and the reaction mixture was purged with argon and refluxed for 12 h under argon. The solution was cooled to r.t. and filtered through a pad of Celite, washed with CH_2Cl_2 and dried with anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9:1) to afford the title compound **7** (75 mg, 63%) as a yellow solid.

Mp 118–120 °C.

IR (ATR): 3306, 3106, 3060, 2858, 2822, 2224, 1926, 1671, 1602, 1542, 1509, 1445, 1222, 1168, 869, 839, 815 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 7.80 (s, 1 H), 7.62 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.30–7.23 (m, 2 H), 7.08–7.01 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.4, 163.1 (d, *J* = 250.0 Hz), 148.5, 141.9, 139.4, 138.0, 137.3, 132.4, 131.0 (d, *J* = 9.0 Hz), 129.4, 128.2 (d, *J* = 3.6 Hz), 118.3, 116.1 (d, *J* = 21.7 Hz), 111.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{11}FNOS$: 308.05399; found: 308.05345.

4-[4,5-Dibromo-2-(4-fluorophenyl)thiophen-3-yl]benzonitrile (8)

Following the general procedure for the decarbonylation–dibromination, after 12 h, compound **8** (41.3 mg, 89%) was obtained as a yellow solid.

Mp 183–185 °C.

IR (ATR): 3074, 2924, 2854, 2233, 1603, 1532, 1507, 1489, 1221, 1185, 1160, 1142, 1102, 1022, 1004, 908, 880, 833, 814 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 7.09–7.02 (m, 2 H), 6.99–6.91 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 249.1 Hz), 141.0, 139.7, 136.2, 132.2, 131.4, 130.7 (d, *J* = 8.1 Hz), 128.2 (d, *J* = 2.8 Hz), 118.5, 116.3, 116.0 (d, *J* = 21.6 Hz), 112.0, 111.2.

GC–MS: *m*/*z* = 436.9 $[M]^+$.

Suzuki Coupling; Typical Procedure

To a dry glass flask purged with argon were added $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (5.1 mg, 0.019 mmol) and dry DME (2 mL). The resulting solution was stirred at r.t. for 10 min, and 3,5-dibromo-2-phenylthiophene (**5**) (25 mg, 0.08 mmol) and Na_2CO_3 (aq) (2 M, 0.65 mL, 1.3 mmol) were added. After 5 min, a solution of phenylboronic acid (23.1 mg, 0.190 mmol) was added and the reaction mixture was purged with argon and refluxed for 12 h under argon. The solution was cooled to r.t. and filtered through a pad of Celite, washed with CH_2Cl_2 and dried with anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to afford the title compound **9** (15 mg, 61%) as a yellow solid.

2,3,5-Triphenylthiophene (9)[20]

Mp 111–116 °C.

IR (ATR): 3059, 3025, 2924, 2853, 1726, 1670, 1598, 1485, 1446, 1252, 1073, 1029, 916, 846, 757 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 2 H), 7.43–7.36 (m, 3 H), 7.35–7.24 (m, 11 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.6, 139.0, 138.0, 136.6, 134.2, 134.1, 129.2, 129.1, 128.9, 128.5, 128.4, 127.6, 127.4, 127.0, 126.5, 125.6.

GC–MS: *m*/*z* = 312.1 $[M]^+$.

3,5-Bis(4-methoxyphenyl)-2-phenylthiophene (10)[16b]

The typical Suzuki coupling procedure was followed. The reaction mixture was refluxed for 12 h. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to afford the title compound **10** (23 mg, 53%) as a yellow solid.

Mp 87–93 °C.

IR (ATR): 3059, 3044, 3000, 2964, 2932, 2837, 1606, 1503, 1458, 1293, 1250, 1176, 1113, 1030, 821, 761 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.54 (m, 2 H), 7.36–7.31 (m, 2 H), 7.29–7.20 (m, 6 H), 6.95–6.90 (m, 2 H), 6.86–6.81 (m, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 158.6, 142.3, 138.5, 136.2, 134.5, 130.1, 129.2, 129.1, 128.4, 127.2, 127.0, 126.9, 125.5, 114.3, 113.8, 55.4, 55.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{21}O_2S$: 373.12568; found: 373.12744.

2-(4-Fluorophenyl)-3,5-bis(4-methoxyphenyl)thiophene (11)

The typical Suzuki coupling procedure was followed. The reaction mixture was refluxed for 12 h. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to afford the title compound **11** (25 mg, 43%) as a yellow oil.

IR (ATR): 3001, 2957, 2922, 2840, 1734, 1675, 1606, 1575, 1552, 1502, 1462, 1294, 1252, 1178, 1034, 830, 738 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.53 (m, 2 H), 7.31–7.26 (m, 2 H), 7.24–7.22 (m, 1 H), 7.22–7.20 (m, 2 H), 6.99–6.91 (m, 4 H), 6.87–6.82 (m, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 245.5 Hz), 159.4, 158.7, 142.3, 138.6, 134.9, 130.8 (d, *J* = 7.2 Hz), 130.6 (d, *J* = 3.6 Hz), 130.1, 128.9, 126.9, 125.4, 115.4 (d, *J* = 21.6 Hz), 114.4, 113.9, 55.4, 55.2.

GC–MS: *m*/*z* = 390.1 $[M]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{19}FO_2S$: 390.10843; found: 390.11016.

3-Bromo-5-(4-methoxyphenyl)-2-phenylthiophene (12)

The typical Suzuki coupling procedure was followed. The reaction mixture was refluxed for 3 h. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to afford the title compound **12** (25 mg, 38%) as a yellow solid.

Mp 89–92 °C.

IR (ATR): 3052, 2999, 2960, 2925, 2842, 1725, 1603, 1573, 1511, 1488, 1457, 1284, 1250, 1179, 1112, 1032, 825, 761 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.67 (m, 2 H), 7.53–7.48 (m, 2 H), 7.47–7.41 (m, 2 H), 7.40–7.34 (m, 1 H), 7.15 (s, 1 H), 6.96–6.90 (m, 2 H), 3.84 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8, 143.2, 136.2, 132.9, 128.8, 128.5, 128.1, 126.8, 126.4, 126.0, 114.4, 107.7, 55.4.

GC–MS: *m*/*z* = 346.0 $[M]^+$ (^{81}Br).

4-(4-Bromo-5-phenyl-2-thienyl)benzonitrile (13)

The typical Suzuki coupling procedure was followed. The reaction mixture was refluxed for 12 h. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9:1) to afford the title compound **13** (49 mg, 54%) as a yellow solid.

Mp 110–112 °C.

IR (ATR): 3056, 2958, 2925, 2855, 1724, 1668, 1603, 1487, 1451, 1331, 1309, 1181, 972, 822, 758 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.60 (m, 6 H), 7.48–7.37 (m, 3 H), 7.34 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.5, 139.6, 137.2, 132.8, 132.2, 129.3, 128.8, 128.7, 128.6, 125.6, 118.5, 111.2, 108.5.

GC–MS: *m*/*z* = 340.9 $[M]^+$ (^{81}Br).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{11}BrNS$: 339.97901; found: 339.97773.

4-[3-(4-Fluorophenyl)-5-phenyl-2-thienyl]benzonitrile (14)

The typical Suzuki coupling procedure was followed. The reaction mixture was refluxed for 12 h. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95:5) to afford the title compound **14** (22 mg, 76%) as a yellow solid.

Mp 99–100 °C.

IR (ATR): 3060, 2958, 2922, 2853, 2225, 1600, 1546, 1499, 1438, 1406, 1214, 1179, 1156, 823, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.65 (m, 5 H), 7.43 (s, 1 H), 7.32–7.29 (m, 4 H), 7.29–7.24 (m, 2 H), 7.03–6.97 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 245.5 Hz), 140.4, 140.1, 138.4, 138.2, 133.4, 132.8, 132.0 (d, *J* = 2.7 Hz), 130.6 (d, *J* = 8.1 Hz), 129.1, 128.7, 128.2, 128.1, 125.7, 118.8, 115.5 (d, *J* = 21.6 Hz), 110.7.

GC–MS: *m*/*z* = 355.1 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{15}FNS$: 356.09037; found: 356.09103.

Computational Details

The calculations using the restricted Kohn–Sham formalism have been performed with the Amsterdam Density Functional (ADF) program package, version 2013.01,[22] with hybrid exchange-correlation approximation B3LYP.[23] Grimme's dispersion (D3) correction has been included.[24] Molecular orbitals (MOs) were expanded in an uncontracted set of Slater-type orbitals (STOs) of triple-ζ quality containing diffuse functions (TZP) and two sets of polarization functions. Only full-electron basis was employed. An auxiliary set of s, p, d, f, and g STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately for each self-consistent field (SCF) cycle. Since ADF utilizes STOs, all integrals are calculated numerically, and thus the results may be sensitive to the quality of the integration grid (Becke grid good was used in all calculations). The geometries of the intermediate species were optimized with the QUILD[25] program using adapted delocalized coordinates until the maximum gradient component was less than 10^{-4} au. Transition state structures were located using linear transit methodology, and then further relaxed with the transition state optimization algorithm. Numerical harmonic frequencies were calculated, and in all cases the nature of the stationary point was confirmed by the presence of either zero or one imaginary frequency modes. The imaginary frequency mode, present in saddle-point transition state structures, was visualized and confirmed to be a reaction coordinate for the bromine addition. Intrinsic reaction coordinate (IRC)[26] methodology was used in order to connect the transition states with σ-complex intermediate structures. In addition, thermochemical properties are derived at *P* = 1 atm and *T* = 298.15 K by using the standard statistical-mechanics relationships for an ideal gas.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562615.

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