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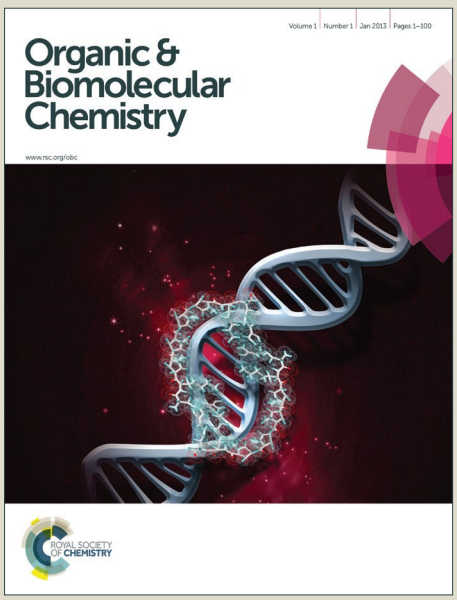

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ARTICLE TYPE

An Efficient Route to Regioselective Functionalization of Benzo[*b*]thiophenes via Palladium-Catalyzed Decarboxylative Heck Coupling Reactions: Insights from Experiment and Computation †

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Pd-catalyzed decarboxylative Heck-type couplings of 3-chlorobenzo[*b*]thiophene-2-carboxylic acids with styrenes have been developed as an effecient strategy for the construction of functionalized benzo[*b*]thiophenes. Theoretical analysis shows that the AgCl generated during the reaction, instead of Pd, π–coordinates with the carboxyl O atom, making easily the rate-determining CO_2 dissociation. The divergent reactivities of the Cl-substituted and H-substituted 3-benzo[*b*]thiophene-2-carboxylic acids are mainly due to the presence of the Cl substituent, which reduces the adjacent π-π interplay, thereby significantly contributing to the decarboxylation. Therefore, the presence of both AgCl and the Cl substituent are of key importance in ensuring the occurence of the reaction under the given conditions.

Introduction

Seeking efficient methods for the construction of C-C bonds has always been a hot topic in the field of synthetic chemistry.[1] Undoubtedly, seeking more mild, practical and selective methods for the formation of C-C bonds has stimulated an impressive number of research interest. Typically, there are four methods for the construction of C-C bonds including nucleophilic substitution, nucleophilic additions, Friedel-Crafts-type reactions and Diels-Alder reactions.[2] It is worth noting that, over 40 years ago, Mizorokil and Heck independently discovered the Pd(0)-catalyzed arylation and vinylation of aryl halides.[3] This developed methodology, known worldwide as the Heck reaction or Mizoroki-Heck reaction, has been emerging as a versatile and powerful tool for the C-C bond formation. Excitingly, because of its tremendous achievements in the C-C bonds formation, it won the 2010 Nobel Prize in chemistry.[4] However, the substrates involved are mainly focus on aryl/vinyl halides or triflates in the Heck-type couplings.[5] Therefore, the development of alternative methods for this elegant transformation has become a challenging but very attractive target to pursue. Recently, exploring efficient, and highly selectivemethods for the direct functionalization of C-H bonds has become a hot topic in organic chemistry. Thus, the direct alkenylation of C(sp2)−H bonds should be more economical and practical. In 2009, Gaunt's group developed a mild and efficient aerobic palladium(II) catalyst system for C2 or C3 alkenylation of pyrroles (Scheme 1a).[6] In the same year, Carretero and co-workers reported an efficient palladium-catalyzed regioselecitve C-2 alkenylation of indoles and pyrroles via C-H bond activation (Scheme 1b).[7] In 2012, Liu et al. demonstrated a convenient and direct palladium-catalyzed olefination of furans and thiopenes by using allylic esters and ethers (Scheme 1c).[8] In 2013, Iitsuka et al. developed an rhodium/silver catalyst system for C3-alkenylation of thiophene and furan-2-carboxylic acids as well as 2-acetylthiophene with acrylates and styrenes (Scheme 1d).[9] On the other hand, carboxylic acid are common and important building blocks, and they are easily prepared from readily available chemicals. As a successful attempt, decarboxylative cross-coupling strategy has been introduced by Gooßen,[10] Myers,[11] and other groups[12] as a reliable tool in the C-C bonds formation. Furthermore, decarboxylative cross-coupling reactions containing DFT studies have also been reported.[13] In 2002, Myers and co-workers initially developed a Pd-catalyzed decarboxylative Heck-type approach for the formation of vinyl arenes.[14] Since then, this new kind of Heck-type coupling reactions have been extensively studied. Nevertheless, investigations on the synthetic strategy using heteroarene carboxylic acids as the coupling partners are limited.[15] Considering the important application of heteroarene compounds in natural products, pharmaceuticals, and material science, it remains a challenge and a high desire to explore new Heck-type coupling scope for heteroarene carboxylic acids.

The benzo[*b*]thiophene skeleton is a key core structure widely found in natural products and drug candidates, and especially promises the extensive applications in material chemistry.[16] Developing novel, efficient and practical methods for the formation or derivatization of benzo[*b*]thiophene motifs is thereby of high ongoing interest.[17] In the present work, we report a new and efficient approach to regioselective alkenylation of benzo[*b*]thiophenes via the palladium-catalyzed decarboxylative Heck-type reactions.

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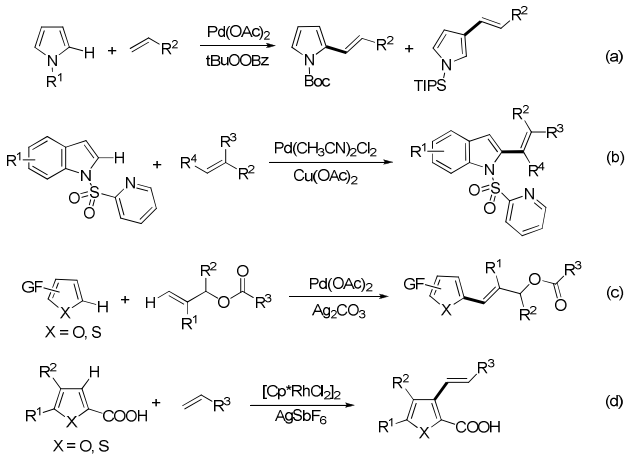
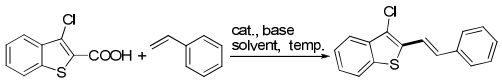


Scheme 1 Strategies for the direct C2 or C3 alkenylation of heterocycles

Results and Discussion

Table 1 Palladium-catalyzed coupling reaction of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid (**1a**) with styrene (**2a**) leading to (*E*)-3-chloro-2-styrylbenzo[*b*]thiophene: optimization of conditions.[a]

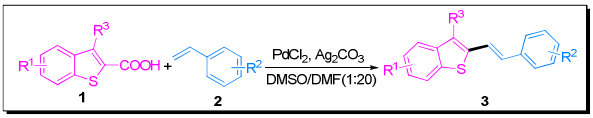


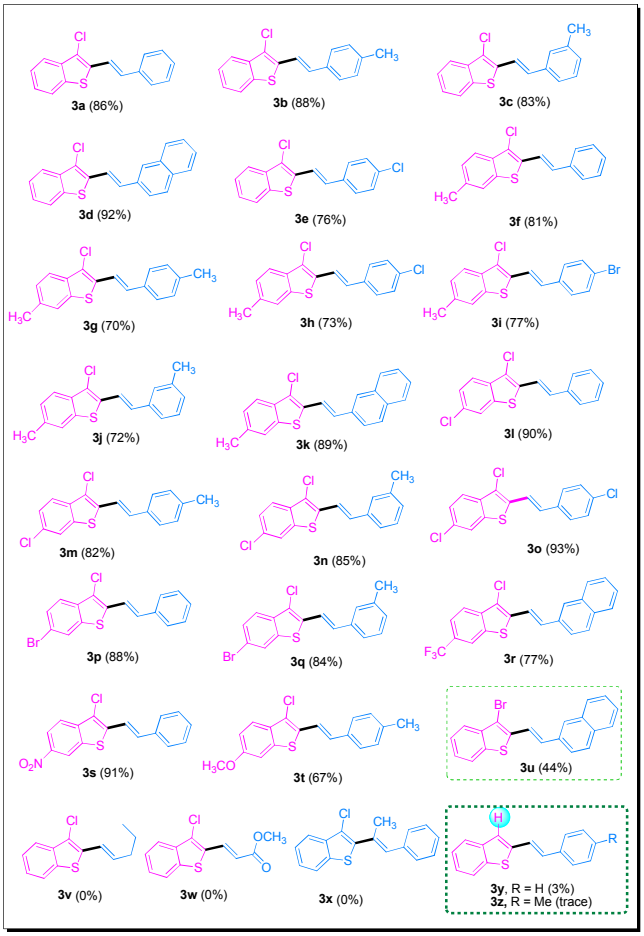
Entry	Cat.	Base	Solvent	Temp. [°C]	Yield [%][b]
1	$PdCl_2$	Ag_2CO_3	DMSO	110	0
2	$PdCl_2$	Ag_2CO_3	DMF	110	20
3	$PdCl_2$	Ag_2CO_3	Toluene	110	5
4	$PdCl_2$	Ag_2CO_3	DMSO/DMF(1:20)	110	86
5	$Pd(OAc)_2$	Ag_2CO_3	DMSO/DMF(1:20)	110	48
6	$Pd(dba)_2$	Ag_2CO_3	DMSO/DMF(1:20)	110	11
7	--	Ag_2CO_3	DMSO/DMF(1:20)	110	0
8	$PdCl_2$	Ag_2O	DMSO/DMF(1:20)	110	37
9	$PdCl_2$	AgOAc	DMSO/DMF(1:20)	110	33
10	$PdCl_2$	Na_2CO_3	DMSO/DMF(1:20)	110	6
11	$PdCl_2$	K_2CO_3	DMSO/DMF(1:20)	110	12
12	$PdCl_2$	Ag_2CO_3	DMSO/DMF(1:20)	80	52

[a] Reaction conditions: 3-chlorobenzo[*b*]thiophene-2-carboxylic acid (**1a**) (0.25 mmol), styrene (**2a**) (0.325 mmol), catalyst (0.0125 mmol), base (0.75mmol), solvent (1.0 mL), reaction time (24 h) under nitrogen atmosphere. [b] Isolated yield.

In order to identify the optimum reaction conditions, the reaction of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid (**1a**) and styrene (**2a**) was chosen as the model reaction. As shown in Table 1, four solvents, DMSO, DMF, toluene and DMSO/DMF were investigated at 110 °C by using 0.05 equiv of $PdCl_2$ as the catalyst, 3 equiv. of Ag_2CO_3 as the base , and 1 mL DMSO/DMF (v_1/v_2=1:20) gave the highest yield (20%) (entries 1-4). The common palladium catalysts, $PdCl_2$, $Pd(OAc)_2$ and $Pd(dba)_2$ were tested in DMSO/DMF (v_1/v_2=1:20) (entries 4-6) using Ag_2CO_3 as the base at 110 °C, and $PdCl_2$ was found to be the most effective catalyst in this reaction. Furthermore, the reaction could not proceed in the absence of the catalyst (entry 7). We attempted to use different bases (compare entries 4, 7-10), and Ag_2CO_3 was superior to the other bases (entry 4). Moreover, further optimization indicated that 110 °C was more suitable for this transformation (entries 4, 11 and 12). After the optimization process of bases, solvents, catalysts and temperature, the benzo[*b*]thiophene derivatives were synthesized under the optimized conditions: 5 mol % $PdCl_2$ as the catalyst, 3 equiv. of Ag_2CO_3 as the base, and 1 mL DMSO/DMF (v_1/v_2=1:20) as the solvent at 110°C under nitrogen atmosphere.

Table 2 Palladium-catalyzed decarboxylative Heck-type couplings of benzo[*b*]thiophene-2-carboxylic acids (1) and styrenes (2) [a, b]





[a] Reaction conditions: the substituted alkenes (1 mmol), molecular iodine (1.5 mmol), H_2O (2 ml), 110°C, 2h, under air atmosphere. [b] Isolated yield.

With the optimized reaction conditions in hand, the scope and generality of the palladium-catalyzed decarboxylative alkenylation of 3-chlorobenzo[*b*]thiophene-2-carboxylic acids was explored, with the results summarized in Table 2. Generally, 3-chlorobenzo[*b*]thiophene-2-carboxylic acids and styrenes that bear electron-donating or withdrawing groups on the aryl rings were compatible with this reaction, and the desired products were obtained in moderate to good yields (Table 2, **3a**-**3q**). Additionally, 2-vinylnaphthalene was also used in this transformation to give the corresponding product **3d** and **3k** in 92% and 89% yield. The decarboxylative cross-coupling reactions could tolerate some functional groups including methyl

(Table 2, **3b**, **3c**, **3f**, **3h**, **3i**, **3j**, **3m**, **3n** and **3q**), methoxy (Table 2, **3t**), C-Cl bond (Table 2, **3a-3q**), and C-Br bond (Table 2, **3i**, **3p**, **3q**), which could be employed for further modification. Notably, strong electron-withdrawing groups such as nitro and trifluoromethyl were also tolerated in the present transformation, and afforded good yields in 77% and 91% respectively. Although aromatic olefins displayed good reactivity, unfortunately, aliphatic and acrylate ones were poor substrates (Table 2, 3v and 3w). Besides that, (*E*)-prop-1-enylbenzene was not a suitable substrate in the present reaction (Table 2, 3x). Interestingly, 3-bromobenzo[*b*]thiophene-2-carboxylic acid also afforded the corresponding product (*E*)-3-bromo-2-(2-(naphthalen-2-yl)vinyl)benzo[*b*]thiophene in 44% yield (Table 2, **3u**). It should be pointed out that the above protocol can be well applied to 3-Cl substituted benzo[*b*]thiophene-2-carboxylic acids but not 3-H substituted ones (Table 2, **3y** and **3z**).

To gain deeper insight into the reaction mechanisms for Pd-catalyzed decarboxylative couplings of styrenes with Cl- and H-substituted substrates, **A**, and H-**A**, respectively, DFT calculations were carried out using the M06 methods.[18] In this section, we presented a mechanism, which featured the involvement of a AgCl molecule generated during the reaction process. And all other possible pathways were collected into Supporting Information.

For the Cl-substituted system, the formation of product **P** (i.e. product **3** in Table 2) involves four key steps in sequence (Figure 1): metalation-depronation (**A→IM2**), decarboxylation (**IM2→IM7**), olefin insertion (**IM7→IM9**), and β-hydride elimination (**IM9→P**). In details, as shown in Figure 1, upon the Pd center coordination with hydroxyl O in **A**, the concerted metalation-depronation was initiated via four-membered transition state **TS1**, affording **IM2** with the exclusion of HCl. The excluded HCl is believed to immediately react with Ag_2CO_3 to give AgCl, which assisted the following processes. It needed to be pointed out here that, once formed, AgCl would smoothly achieve the metalation-depronation process with a relative free energy of only 17.3 kcal/mol (**IM11** in Figure 2), which is substantially lower than that for the transformation **A→IM2** (29.1 kcal/mol corresponding to **TS1** in Figure 1).

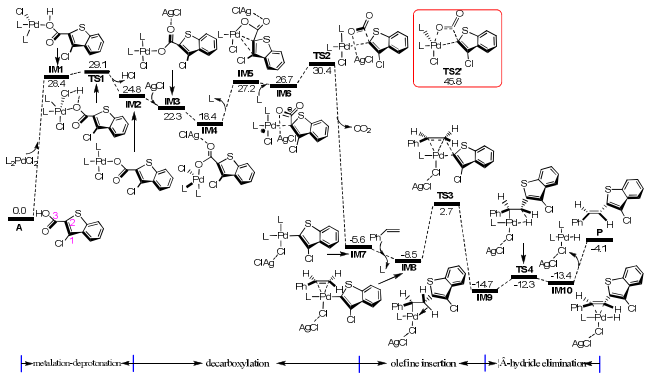
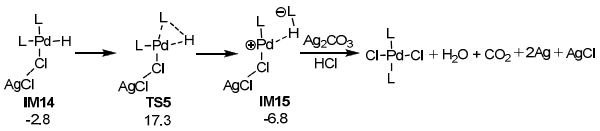


Figure 1 Calculated free energy profiles in DMF solution for the formation of P from the reaction of the Cl-substituted substrate A with styrene as well as schematic structures of intermediates and transition states involved (L =DMSO). The relative free energies are given in kcal/mol. a **TS2**' is a decarboxylation transition state with no involvement of AgCl, corresponding to **TS2**

Therefore, in the following catalytic cycles, the metalation-depronation route with the involvement of AgCl in Figure 2 (**A→IM11**) was considered to be the favored one. The decarboxylation step started with the coordination of AgCl to the carbonyl O atom of **IM2** and forms **IM3**. To facilitate the subsequent π-coordination of Pd with C1=C2 double bond, **IM3** isomerized into slightly more stable **IM4** by rotating the Pd-O single bond along the C3-O(Pd) σ-bond. The tandem dissociation and association of one DMSO ligand is then followed to get an energy-rich intermediate **IM6**. From **IM6**, the reaction underwent the dissociation of CO_2 through **TS2** with an energy demand of 3.7 kcal/mol and generated a 16-electron species **IM7**, which lay 5.6 kcal/mol below the reaction entrance. After the dissociation of one DMSO ligand from **IM7**, the styrene occupied the site left by the dissociated DMSO ligand to give slightly more stable species **IM8**, with the π-coordination of the phenylethylene C=C bond moiety with the Pd center. And next, the olefine insertion into the Pd-C2 bond occurs via transition state **TS3**, giving rise to intermediate **IM9**. The barrier involved in this olefine insertion step was calculated to be 11.2 kcal/mol. Through **TS4** with a small barrier of 2.4 kcal/mol, the β-hydride elimination takes place by the migration of one H(CC2) atom to the Pd atom, resulting in product **P**, from which L_2PdHCl (L = DMSO) and AgCl was simultaneously liberated. In order to initiate the Pd catalyst regeneration (**IM14**→L_2PdCl_2) for the next reaction procedures, as indicated in Scheme 2, the reductive elimination of HL in **IM14** occured with a barrier of 20.1 kcal/mol to become Pd(0) intermediate **IM15**, that was then oxidized by the oxidant Ag_2CO_3 in the presence of HCl to form L_2PdCl_2.



Scheme 2 The Pd catalyst regeneration pathway. The relative free energies in are given in kcal/mol.

According to the results above, it was seen that the decarboxylation had an overall barrier of 30.4 kcal/mol, in contrast to 29.1 kcal/mol of metalation-depronation, 11.2 kcal/mol of olefine insertion, 2.4 kcal/mol of β-hydride elimination, and 20.1 kcal/mol of catalyst regeneration. Therefore, the decarboxylation with the involvement of AgCl is the rate-determining step along the reaction coordinate, consistent with that of the direct decarboxylation pathway with no assistor.[18-20] However, the energy barrier value calculated for the former (30.4 kcal/mol) was apparently much lower than that for the latter in Figure 1 (45.8 kcal/mol corresponding to **TS2'**). The preference for the decarboxylation in the presence of AgCl over the case in the absence of AgCl is likely ascribed to the fact that the π–coordination of Ag instead of Pd with the carboxyl O atom reduces the Pd-O π–interaction, thus resulting in easier dissociation of CO_2 as compared to the decarboxylation with no AgCl involvement. Therefore, the presence of AgCl plays critical role in ensuring the proceeding of the reaction under the given

conditions.

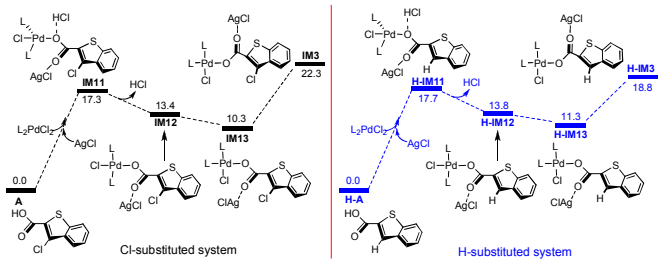


Figure 2 Calculated free energy profiles in DMF solution for the Cl- and H-substituted metalation-depronation process with the involvement of AgCl as well as schematic structures of intermediates and transition states involved (L =DMSO). The relative free energies are given in kcal/mol.

In the case of the H-substituted system, as illustrated in Figure 3, the intermediates and transition states were marked with the capital letter "H" in the left superscript in order to differentiate them from those with the Cl substituted version. It was found that the H-substituted system involved the same mechanisms and rate-determining step to the Cl-substituted system discussed above. Thus, the relevant mechanism details are not discussed again for simplification.

In order to elucidate the different reactivity of two substrates **A** and **H-A**, we compared the overall barriers for the rate-determining steps (i.e., decarboxylation) of the two reactions. It was observed in Figure 3 that the overall barrier of the decarboxylation step for the H-substituted system was 32.8 kcal/mol (the energy difference between **H-TS2** and **H-A**), which was 2.4 kcal/mol greater than that (30.4 kcal/mol) for the Cl-substituted system in Figure 1 (the energy difference between **TS2** and **A**). This result was consistent with the experimental finding that Cl-substituted substrate **A** brings out the product **P** in 86% yield, whereas, upon replacement of the Cl substituent by a hydrogen atom, the H-substituted product **H-P** is achieved in only 3% yield.

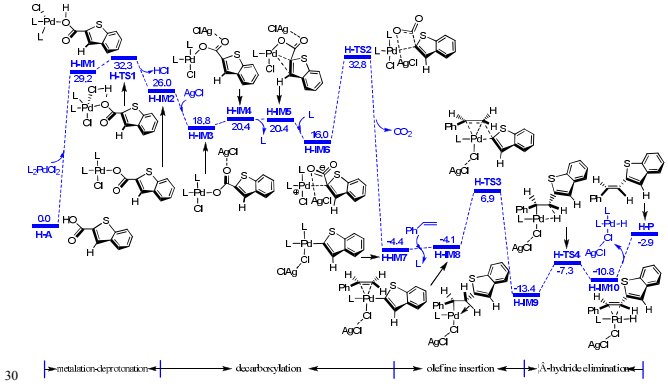
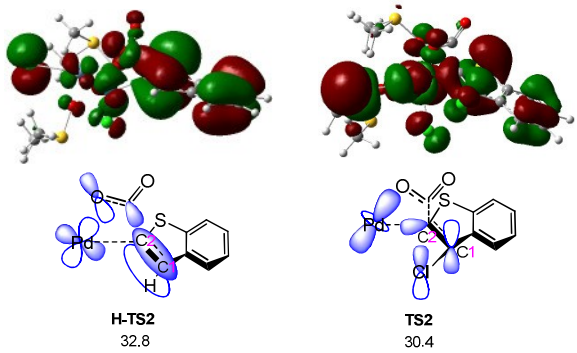


Figure 3 Calculated free energy profiles in DMF solution for the formation of **H-P** from the reaction of the H-substituted substrate **H-A** with phenylethylene as well as schematic structures of intermediates and transition states involved (L =DMSO). The relative free energies are given in kcal/mol.

We could understand the fact above by analyzing the frontier molecular orbitals of **TS2** and **H-TS2**. Scheme 3 showed the highest occupied molecular orbitals (HUMOs) calculated for these two structures. In the HUMO of **H-TS2**, it was clear that the C2 atom uses its sp^2-hybridized orbital to interact in a σ bonding fashion with the C π* orbital of the CO_2 moiety. In contrast, in the HUMO of **TS2**, the p-π orbital of the C2 atom interacted with the Pd center. Clearly, the presence of Cl substituent in **TS2** reduces the π-π interplay between C1 and C2 atoms and thereby strengthens the orbital overlaps of C2 atom and the Pd center, thus contributing the Pd···C2 bonding and the C2-C(O_2) bond cleavage. These results point to the fact that the introduction of Cl substituent is of key importance for the stability of the decarboxylation transition state **TS2**, which makes the CO_2 dissociation more accessible than that for the H-substituted system.



Scheme 3 Diagrams of the HUMOs of two decarboxylation transition states, H-TS2 and TS2. For clarity, AgCl is omitted in the schematic diagrams. The relative free energies are given in kcal/mol.

Couclusions

In summary, we have successfully developed a Pd-catalyzed decarboxylative Heck-type coupling reaction for the highly regioselective alkenylation of 3-chlorobenzo[*b*]thiophene-2-carboxylic acids, providing an alternative approach for the formation of diverse benzo[*b*]thiophenes. Theoretical studies indicate that the involvement of AgCl generated during the reaction process is of key importance for the proceeding of the transformation. The greater reactivity of Cl substituted 3-benzo[*b*]thiophene-2-carboxylic acids over H-substituted ones is closely related to the presence of the Cl substituent, which can reduce adjacent π-π interaction, thus resulting in the facile decarboxylation as compared to the H substituent.

Experimental section

General information and materials

All commercially available reagent grade chemicals were purchased from chemical suppliers and used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400 MHz or 500 MHz spectrometer with TMS as internal standard (400 MHz ^{1}H, 100 MHz ^{13}C; 500 MHz ^{1}H, 125 MHz ^{13}C) at room temperature, the chemical shifts (δ) were expressed in ppm and J values were given in Hz. Microanalyses were carried out using chemical ionization method under atmospheric pressure (APCI). Column chromatography was performed on silica gel (200-300 mesh).

Computational Methods

All calculations presented in this work were carried out using M06 functional[18] with the Gaussian 09 suite of programs,[21] which had been shown to describe static Pd-mediated organometallic systems reasonably well.[22, 23, 24] The SDD[25, 26] basis set with the effective core potential was used for Pd, Ag, S, and Cl atoms, while the 6-31G(d,p) basis set was used for the remaining atoms. Geometry optimizations was conducted at the chosen level of theory, and the intrinsic reaction coordinate (IRC) analysis[27] from the transition states had been followed to confirm that such structures actually connected the two relevant minima. Frequency calculations at the same level of theory were also carried out to verify all the stationary points as minima (zero imaginary frequencies) or first-saddle points (one imaginary frequency) and to provide free energies at 298.15 K, which include entropic contributions by considering the vibrations, rotations, and translations of the species.

Solvent effects have been introduced via single-point calculations on gas-phase-optimized geometries by employing the simple self-consistent reaction field (SCRF) method[28, 29, 30] based on CPCM solvation model[31] with UAKS cavities.[32] The single-point energy calculations were performed using the larger basis set, i.e., SDD for Pd, Ag, S, and Cl atoms and 6-311+G(d,p) for the other atoms. Here, acetonitrile was used as solvent, corresponding to the experimental conditions. In this paper, relative free energies in solution were exclusively used to describe the reaction mechanism throughout the study.

General experimental procedures.

A 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with $PdCl_2$ (2.2 mg), Ag_2CO_3 (205.3 mg), substituted 3-chlorobenzo[*b*]thiophene-2-carboxylic acids (**1**) (0.25 mmol) and styrenes (**2**) (0.325 mmol). The tube was evacuated twice and backfilled with nitrogen, and DMSO/DMF (v_1/v_2=1:20) (1.0 mL) was added to the tube under nitrogen atmosphere. The tube was sealed with a balloon and then the mixture was allowed to stir under nitrogen atmosphere at 110 ^oC for 24 h. After completion of the reaction, the resulting solution was cooled to room temperature, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product (**3**).

(*E*)-3-Chloro-2-styrylbenzo[*b*]thiophene (3a): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp 139-141^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.82 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.60 (d, 2H, J = 8.0 Hz), 7.55 (d, 1H, J = 16.0 Hz), 7.46-7.41 (m, 4H), 7.36 (d, 1H, J = 8.0 Hz), 7.07 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.4, 136.4, 136.1, 135.6, 132.3, 128.8, 128.5, 126.9, 126.0, 125.1, 122.4, 121.8, 119.6, 119.0. MS (APCI) *m/z*=271 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}ClS$: C, 70.97; H, 4.09; Cl, 13.09; S, 11.84. Found C, 70.94; H, 4.07; Cl, 13.10; S, 11.82.

(*E*)-3-Chloro-2-(4-methylstyryl)benzo[*b*]thiophene (3b): Eluent petroleum ether/ethyl acetate (35:1). White solid, mp 145-146 ^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.80 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 8.0 Hz), 7.48 (d, 2H, J = 8.0 Hz), 7.46-7.38 (m, 2H), 7.20 (d, 2H, J = 8.0 Hz), 7.05 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.6, 137.5, 135.9, 135.8, 133.7, 132.3, 129.5, 126.8, 125.8, 125.1, 122.4, 121.7, 119.2, 118.0. MS (APCI) *m/z*=285 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}ClS$: C, 71.69; H, 4.60; Cl, 12.45; S, 11.26. Found C, 71.65; H, 4.62; Cl, 12.43; S, 11.23.

(*E*)-3-Chloro-2-(3-methylstyryl)benzo[*b*]thiophene (3c): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp 110-112 ^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.81 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 16.0 Hz), 7.47-7.39 (m, 4H), 7.31 (t, 1H, J = 8.0 Hz), 7.16 (d, 1H, J = 8.0 Hz), 7.05 (d, 1H, J = 16.0 Hz), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.4, 137.5, 136.4, 136.0, 135.7, 132.4, 129.3, 128.7, 127.5, 125.9, 124.1, 122.4, 121.7, 119.5, 118.8, 21.4. MS (APCI) *m/z*=285 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}ClS$: C, 71.69; H, 4.60; Cl, 12.45; S, 11.26. Found C, 71.65; H, 4.62; Cl, 12.43; S, 11.23.

(*E*)-3-Chloro-2-(2-(naphthalen-2-yl)vinyl)benzo[*b*]thiophene (3d): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp 151-153 ^oC. δ ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.93 (s, 1H), 7.89-7.78 (m, 6H), 7.66 (d, 1H, J = 16.0 Hz), 7.54-7.50 (m, 2H), 7.48-7.40 (m, 2H), 7.25 (d, 1H, J = 16.0 Hz), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.5, 136.1, 135.7, 133.9, 133.6, 133.4, 132.3, 128.5, 128.2, 127.8, 127.4, 126.5, 126.4, 126.0, 125.1, 123.4, 122.4, 121.8, 119.7, 119.3. MS (APCI) *m/z*=321 $[M+H]^+$. Anal. Calcd for $C_{20}H_{13}ClS$: C, 74.87; H, 4.08; Cl, 11.05; S, 9.99. Found C, 74.72; H, 4.11; Cl, 11.13; S, 9.84.

(*E*)-3-Chloro-2-(4-chlorostyryl)benzo[*b*]thiophene (3e): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp 156-158 ^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.81 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.52-7.48 (m, 3H), 7.45-7.40 (m, 2H), 7.37 (d, 2H, J = 8.0 Hz), 7.00 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.4, 136.1, 135.2, 134.9, 134.1, 130.8, 129.0, 128.0, 126.2, 125.2, 122.4, 121.9, 120.0, 119.6. MS (APCI) *m/z*=305 $[M+H]^+$. Anal. Calcd for $C_{16}H_{10}Cl_2S$: C, 62.96; H, 3.30; Cl, 23.23; S, 10.51. Found C, 62.87; H, 3.31; Cl, 23.26; S, 10.64.

(*E*)-3-Chloro-6-methyl-2-styrylbenzo[*b*]thiophene (3f): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp 131-133 ^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.68 (d, 1H, J = 8.0 Hz), 7.59-7.57 (m, 3H), 7.52 (d, 1H, J = 16.0 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 136.6, 136.3, 136.2, 135.3, 134.4, 131.6, 128.8, 128.3, 126.8, 122.3, 121.4, 119.5, 119.2, 21.6. MS (APCI) *m/z*=285 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}ClS$: C, 71.69; H, 4.60; Cl, 12.45; S, 11.26. Found C, 71.62; H, 4.57; Cl, 12.36; S, 11.16.

(*E*)-3-Chloro-6-methyl-2-(4-methylstyryl)benzo[*b*]thiophene (3g): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 144-145 ^oC. ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.67 (d, 1H, J = 8.0 Hz), 7.56 (s, 1H), 7.48-7.45 (m, 3H), 7.28-7.20 (m, 3H), 7.01 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.4, 136.2, 136.1, 135.3, 134.7, 133.8, 131.6, 129.5, 126.8, 126.7, 122.3, 121.3, 119.1, 118.2, 21.6, 21.3. MS (APCI) *m/z*=299 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}ClS$: C, 72.35; H, 5.06; Cl, 11.86; S, 10.73. Found C, 72.28; H, 5.11; Cl, 11.92; S, 10.64.

(*E*)-3-Chloro-2-(4-chlorostyryl)-6-methylbenzo[*b*]thiophene (3h): Eluent petroleum ether/ethyl acetate (40:1). White solid, mp

161-162 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.68 (d, 1H, J = 8.0 Hz), 7.56 (s, 1H), 7.50-7.46 (m, 3H), 7.36 (d, 2H, J = 8.0 Hz), 7.26 (d, 1H, J = 8.0 Hz), 6.95 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 136.5, 136.3, 135.2, 135.1, 134.0, 133.9, 130.1, 129.0, 127.9, 127.0, 122.3, 121.5, 120.0, 119.7, 21.6. MS (APCI) *m/z*=319 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}Cl_2S$: C, 63.96; H, 3.79; Cl, 22.21; S, 10.04. Found C, 63.99; H, 3.72; Cl, 22.23; S, 10.13.

(E)-2-(4-Bromostyryl)-3-chloro-6-methylbenzo[b]thiophene (3i): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 171-173 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.68 (d, 1H, J = 8.0 Hz), 7.56 (s, 1H), 7.53-7.41 (m, 5H), 7.26 (d, 1H, J = 8.0 Hz), 6.94 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 136.6, 136.3, 135.5, 135.2, 134.0, 131.9, 130.2, 128.2, 126.9, 122.3, 122.1, 121.5, 120.0, 119.8, 21.6. MS (APCI) *m/z*=340, 342 $[M+K]^+$. Anal. Calcd for $C_{17}H_{12}BrClS$: C, 56.14; H, 3.33; Br, 21.97; Cl, 9.75; S, 8.82. Found C, 56.21; H, 3.24; Br, 21.91; Cl, 9.85; S, 8.84.

(*E*)-3-Chloro-6-methyl-2-(3-methylstyryl)benzo[*b*]thiophene (3j): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 146-147 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.68 (d, 1H, J = 8.0 Hz), 7.56 (s, 1H), 7.51 (d, 1H, J = 16.0 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.32-7.25 (m, 2H), 7.15 (d, 1H, J = 8.0 Hz), 7.01 (d, 1H, J = 16.0 Hz), 2.51 (s, 3H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.4, 136.5, 136.3, 135.3, 134.6, 131.8, 129.2, 128.7, 127.4, 126.8, 124.0, 122.3, 121.4, 119.4, 118.9, 21.6, 21.4. MS (APCI) *m/z*=299 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}ClS$: C, 72.35; H, 5.06; Cl, 11.86; S, 10.73. Found C, 72.28; H, 5.11; Cl, 11.92; S, 10.64.

(*E*)-3-Chloro-6-methyl-2-(2-(naphthalen-2-yl)vinyl)benzo[*b*]thiophene (3k): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 162-164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.92 (s, 1H), 7.87 (d, 1H, J = 8.0 Hz), 7.84-7.78 (m, 2H), 7.69 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 16.0 Hz), 7.59 (s, 1H), 7.52-7.49 (m, 2H), 7.27 (d, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 16.0 Hz), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 136.4, 136.3, 135.3, 134.5, 134.1, 133.6, 133.3, 131.7, 128.5, 128.2, 127.8, 127.3, 126.8, 126.5, 126.3, 123.4, 122.4, 121.4, 119.6, 119.4, 21.7. MS (APCI) *m/z*=335 $[M+H]^+$. Anal. Calcd for $C_{21}H_{15}ClS$: C, 75.32; H, 4.52; Cl, 10.59; S, 9.58. Found C, 75.27; H, 4.41; Cl, 10.63; S, 9.51.

(*E*)-3,6-Dichloro-2-styrylbenzo[*b*]thiophene (3l): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 128-129 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.16 (s, 1H), 7.70 (d, 1H, J = 8.0 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 16.0 Hz), 7.44-7.40 (m, 3H), 7.35 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.0, 136.2, 136.1, 136.0, 132.7, 132.1, 128.9, 128.6, 126.9, 126.0, 122.6, 122.0, 119.2, 118.7. MS (APCI) *m/z*=305 $[M+H]^+$. Anal. Calcd for $C_{16}H_{10}Cl_2S$: C, 62.96; H, 3.30; Cl, 23.23; S, 10.51. Found C, 62.87; H, 3.31; Cl, 23.26; S, 10.64.

(*E*)-3,6-Dichloro-2-(4-methylstyryl)benzo[*b*]thiophene (3m): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 135-136 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.47 (s, 1H), 7.69 (d, 1H, J = 8.0 Hz), 7.48-7.38 (m, 4H), 7.22 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 16.0 Hz), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.8, 136.9, 136.4, 136.0, 133.5, 132.7, 131.9, 129.6, 126.8, 125.9, 122.5, 122.0, 118.8, 117.7, 21.4. MS (APCI) *m/z*=319 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}Cl_2S$: C, 63.96; H, 3.79; Cl, 22.21; S, 10.04. Found C, 63.99; H, 3.72; Cl, 22.23; S, 10.13.

(*E*)-3,6-Dichloro-2-(3-methylstyryl)benzo[*b*]thiophene (3n): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 139-141 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.75 (s, 1H), 7.70 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 16.0 Hz), 7.41-7.37 (m, 3H), 7.31 (t, 1H, J = 8.0 Hz), 7.16 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 16.0 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.5, 136.9, 136.2, 136.1, 136.0, 132.9, 132.0, 129.5, 128.7, 127.5, 126.0, 124.1, 122.5, 122.0, 119.0, 118.5, 21.4. MS (APCI) *m/z*=319 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}Cl_2S$: C, 63.96; H, 3.79; Cl, 22.21; S, 10.04. Found C, 63.99; H, 3.72; Cl, 22.23; S, 10.13.

(*E*)-3,6-Dichloro-2-(4-chlorostyryl)benzo[*b*]thiophene (3o): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 157-159 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.75 (s, 1H), 7.70 (d, 1H, J = 8.0 Hz), 7.50 (d, 2H, J = 8.0 Hz), 7.45 (d, 1H, J = 16.0 Hz), 7.42-7.37 (m, 3H), 6.99 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.0, 135.9, 135.7, 134.7, 134.3, 132.3, 131.2, 129.1, 128.0, 126.1, 122.7, 122.1, 119.6, 119.3. MS (APCI) *m/z*=338 $[M+H]^+$. Anal. Calcd for $C_{16}H_9Cl_3S$: C, 56.58; H, 2.67; Cl, 31.11; S, 9.44. Found C, 56.51; H, 2.76; Cl, 31.06; S, 9.45.

(*E*)-6-Bromo-3-chloro-2-styrylbenzo[*b*]thiophene (3p): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 161-162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.91 (s, 1H), 7.64 (d, 1H, J = 8.0 Hz), 7.58 (d, 2H, J = 8.0 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 16.0 Hz), 7.42 (t, 2H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 16.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.3, 136.3, 136.2, 136.1, 132.8, 128.9, 128.7, 128.6, 126.9, 124.9, 122.8, 119.9, 119.3, 118.7. MS (APCI) *m/z*=348, 350 $[M+H]^+$. Anal. Calcd for $C_{16}H_{10}BrClS$: C, 54.96; H, 2.88; Br, 22.85; Cl, 10.14; S, 9.17. Found C, 54.91; H, 2.96; Br, 22.89; Cl, 10.03; S, 9.11.

(*E*)-6-Bromo-3-chloro-2-(3-methylstyryl)benzo[*b*]thiophene (3q): Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 178-181 °C. δ ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.91 (s, 1H), 7.64 (d, 1H, J = 8.0 Hz), 7.54 (d, 2H, J = 8.0 Hz), 7.47 (d, 1H, J = 16.0 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.16 (d, 1H, J = 8.0 Hz), 7.04 (d, 1H, J = 16.0 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 138.5, 137.3, 136.3, 136.2, 136.1, 132.9, 129.5, 128.8, 128.6, 127.6, 124.9, 124.1, 122.8, 119.8, 119.1, 118.4. MS (APCI) *m/z*=340, 342 $[M+K]^+$. Anal. Calcd for $C_{17}H_{12}BrClS$: C, 56.14; H, 3.33; Br, 21.97; Cl, 9.75; S, 8.82. Found C, 56.21; H, 3.24; Br, 21.91; Cl, 9.85; S, 8.84.

(*E*)-3-chloro-2-(2-(naphthalen-2-yl)vinyl)-6-(trifluoromethyl)benzo[*b*]thiophene (3r): Eluent petroleum ether/ethyl acetate (25:1). White solid, mp 168-170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 8.02 (s, 1H), 7.91 (s, 1H), 7.85-7.81 (m, 4H), 7.76 (d, 1H, J = 10.0 Hz), 7.64-7.58 (m, 2H), 7.49 (t, 2H, J = 5.0 Hz), 7.24 (d, 1H, J = 10.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 139.8, 139.0, 135.8, 133.9, 133.6(q, J=36.3), 128.7, 128.3, 128.1, 127.9, 127.8, 127.7, 126.7, 126.4 (q, J=270.1), 125.3, 123.2, 122.1, 121.9 (d, J=3.7), 119.8, 119.3, 118.7. MS (APCI) *m/z*=389.0 $[M+H]^+$. Anal. Calcd for $C_{21}H_{12}ClF_3S$: C, 64.87; H, 3.11; Cl, 9.12; F, 14.66; S, 8.25. Found C, 64.81; H, 3.06; Cl, 9.04; F, 14.57; S, 8.16.

(*E*)-3-chloro-6-nitro-2-styrylbenzo[*b*]thiophene (3s): Eluent petroleum ether/ethyl acetate (20:1). yellow solid, mp 147-149 °C. δ ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.74-7.71 (m, 3H), 7.67 (s, 1H), 7.56 (d, 1H, J = 10.0 Hz), 7.40-7.35 (m, 2H), 6.81 (dd, 1H, J = 10.0 Hz), 5.80 (d, 1H, J = 20.0 Hz), 5.26 (d, 1H, J = 20.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 135.9, 134.0, 132.5, 132.1, 127.1, 127.0, 126.6, 125.3, 125.2, 124.9, 122.1, 113.1. MS (APCI) *m/z*=316 $[M+H]^+$. Anal. Calcd for $C_{16}H_{10}ClNO_2S$: C, 60.86; H, 3.19; Cl, 11.23; N, 4.44; O, 10.13; S, 10.15. Found C, 60.63; H, 3.27; Cl, 11.08; N, 4.37; O, 10.16; S, 10.42.

(*E*)-3-chloro-5-methoxy-2-(4-methylstyryl)benzo[*b*]thiophene (3t): Eluent petroleum ether/ethyl acetate (30:1). white solid, mp 116-118 °C. δ ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.57 (d, 1H, J = 5.0 Hz), 7.45-7.41 (m, 3H), 7.19-7.15 (m, 3H), 7.01-6.98 (m, 2H), 3.89 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 171.2, 158.2, 138.5, 138.4, 137.0, 133.7, 132.0, 129.5, 128.9, 126.8, 123.2, 118.1, 116.2, 103.7, 55.6, 21.1. MS (APCI) *m/z*=315 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}ClOS$: C, 68.67; H, 4.80; Cl, 11.26; O, 5.08; S, 10.18. Found C, 68.46; H, 4.59; Cl, 11.19; O, 5.14; S, 10.09.

(*E*)-3-bromo-2-(2-(naphthalen-2-yl)vinyl)benzo[*b*]thiophene (3u): Eluent petroleum ether/ethyl acetate (30:1). white solid, mp 172-174 °C. δ ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.90 (s, 1H), 7.86-7.82 (m, 3H,), 7.80-7.75 (m, 3H), 7.62 (d, 1H, J = 15.0 Hz), 7.51-7.48 (m, 2H), 7.43 (t, 1H, J=5.0 Hz), 7.38 (t, 1H, J=5.0 Hz), 7.25 (d, 2H, J=10.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 138.9, 137.4, 136.5, 133.9, 133.6, 133.4, 132.8, 128.6, 128.2, 127.8, 127.5, 126.6, 126.4, 126.1, 125.3, 123.4, 123.1, 122.3, 120.9. MS (APCI) *m/z*=365, 367 $[M+H]^+$. Anal. Calcd for $C_{20}H_{13}BrS$: C, 65.76; H, 3.59; Br, 21.87; S, 8.78. Found C, 65.66; H, 3.47; Br, 21.83; S, 8.69.

(*E*)-2-Styrylbenzo[*b*]thiophene (3y):[33] Eluent petroleum ether/ethyl acetate (30:1). White solid, mp 83-84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.80 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.42-7.31 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 142.9, 140.2, 138.9, 136.6, 130.9, 128.8, 128.0, 126.6, 124.7, 124.5, 123.4, 123.3, 122.3, 122.2. MS (APCI) *m/z*=237 $[M+K]^+$. Anal. Calcd for $C_{17}H_{12}BrClS$: C, 81.31; H, 5.12; S, 13.57; found C, 81.27; H, 5.15; S, 13.59.

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