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An efficient phosphine-free palladium coupling for the synthesis of new 2-arylbenzo[*b*]thiophenes

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Abstract—Straightforward and rapid access to 2-arylbenzo[*b*]thiophenes has been developed. It involved a catalytic coupling of 3-activated benzo[*b*]thiophenes with several aryl halides in the presence of a phosphine-free palladium system. In case of fragile functional groups such as aldehydes, a quaternary ammonium was used as an additive as with the other substrates, the coupling performed better and faster in the presence of a crown ether, the best one being DCH-18-C-6, with good yields and low reaction times. This method would provide a direct access to novel structures of biological interest.

1. Introduction

The benzo[*b*]thiophene core was found to be present in several drug candidates, exhibiting some interesting biological properties, e.g. antipsychotic,[1] antiinflammatory,[2] antiallergic,[3] antithrombotic-fibrilonitic[4] and herpes virus inhibitor.[5]

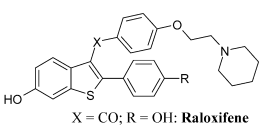
A particular interest was given to 2-arylbenzo[*b*]thiophenes for the treatment of various cancers. Indeed, some derivatives were found to be potent selective estrogen receptor modulators (SERMs)[6]—the most famous of which being Raloxifene and Arzoxifene (Fig. 1)—also used as antitubulin agents.[7,8]

The recent interest to this class of compounds lead to the investigation of new synthetic routes to substituted benzo[*b*]thiophenes. An intramolecular cyclisation from substituted thiobenzyls was generally used, according to the procedure described by Kost.[9] However, this method, which involved two steps, one basic and the following acidic, proved to be non-regioselective and was not compatible with acid or base sensitive functional groups. Thus, other methods were developed, starting from thiobenzyl[10] or thioanisole[11] derivatives. Recently, Flynn et al. described an efficient synthesis of 2,3-disubstituted benzo[*b*]thiophenes with tubulin binding activity.[12] However, even if the synthetic path afforded the desired products in high yields, no more than seven steps were required. Consequently, catalytic routes were investigated for direct access to 2-arylbenzo[*b*]thiophenes. For instance, Sall[13] and Samat[14] have synthesised some of these derivatives by Suzuki coupling.[15]

We focused on a method allowing the direct arylation of benzo[*b*]thiophenes. On the contrary to the usual arylation methods,[16] of the Stille,[17] Kumada[18] and Suzuki-type,[15] which all involve a regioselective halogenation of the substrate and the use of an organometallic reagent prior to the coupling, the 'Heck-type' coupling is carried out in one single step. Indeed, Miura[19] and Otha[20] previously managed to arylate benzo[*b*]thiophene selectively in moderate yields with palladium, triphenylphosphine and, for the first one, an over stoechiometric (i.e. 2 equiv.) amount of copper iodide.

We have recently reported the direct arylation of 3-substituted benzo[*b*]thiophenes[21] based on the improvements of a catalytic coupling previously developed on thiophene derivatives.[22,23]

It involved the use of a system based on $Pd(OAc)_2$, *n*-Bu_4NBr, an inorganic base (K_2CO_3) in a polar aprotic solvent, DMF being the most suitable.[24] In this paper, we will describe the extensions of this method as well as some improvements achieved in order to develop an easy parallel



X = CO; R = OH: **Raloxifene**
X = O; R = OMe: **Arzoxifene**

Figure 1.

Keywords: Benzo[*b*]thiophene; Heck-type aryl coupling; Palladium catalysis.
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synthesis of valuable new benzo[*b*]thiophene derivatives for biological studies.

2. Results and discussion

2.1. Synthesis of the starting materials

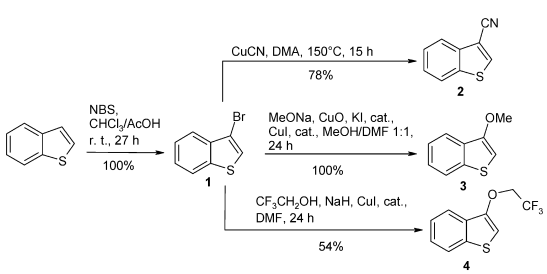
The 3-bromobenzo[*b*]thiophene **1** was quantitatively and selectively synthesised by direct bromination of benzo[*b*]thiophene with *N*-bromosuccinimide under acidic conditions, according to a procedure described by Kellogg.[25] Then, a nucleophilic aromatic substitution with copper cyanide[26] afforded benzo[*b*]thiophene-3-carbonitrile **2** in 78% yield. Similarly, according to a procedure previously described by our group,[27] 3-methoxybenzo[*b*]thiophene **3** and 3-(2,2,2-trifluoroethoxy)-benzo[*b*]thiophene **4** were synthesised in 100 and 54% yields, respectively (Scheme 1).

2.2. Coupling studies and improvements

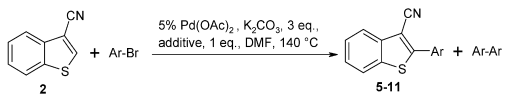
The following Heck-type coupling required an aromatic halide and a catalytic system based on palladium salt. We have previously described this coupling with a system based on the use of 5% of palladium diacetate, a stoiechiometric amount of tetra-*n*-butylammonium bromide, an excess of potassium carbonate in DMF (Scheme 2).[21]

The reaction conditions have already been studied a few years ago by our group.[24] Among species of $Pd^{(0)}$ and $Pd^{(II)}$, $Pd(OAc)_2$ was found to give the best yields. Following the Jeffery conditions,[28] we also used a quaternary ammonium additive which enhanced the reaction rates and improved the yields, although the nature of its effect was not proved (formation of a very reactive palladium complex, better homogenisation of the reactants?). Amatore and Jutand have reported[29] that the quaternary ammonium would increase the salinity of the mixture. Palladium species may then be stabilised by halide ions.

It was also reported that the whole catalytic system only slightly differed from the one used for the Ullmann[30] catalytical coupling by the nature of the base (potassium carbonate instead of diisopropylethylamine).[31] Therefore, various amounts of biaryl product (Ar–Ar) could be obtained. In addition, supposing that the basicity would affect the conversion and the reaction rate, the quaternary ammonium was replaced by a crown ether, that of being dicyclohexyl-18-crown-6 (DCH-18-C-6). We used four different phenyl bromides, three of them bearing a chlorine atom at different positions and one bearing a cyano group at the *ortho* position (Table 1).



Scheme 1.



Scheme 2.

In most cases, better conversions (and also better isolated yields) were observed in the case of the additive being the crown ether. The reaction was found in all cases to be more selective towards the formation of the biaryl by-products and, especially in the case of 2-bromobenzonitrile (entry 4), the reaction was much faster.

We then performed this coupling on a heteroaryl halide, the first one being 2-bromopyridine (Table 2 entries 1–5). We assumed that this substrate would relatively be non-reactive due to its tendency to easily form 2,2′-bipyridine as previously observed during the Ullmann coupling.[31] Although little selective, the Heck-type coupling performed to afford the major desired product **9**. Reaction times were divided by 5 when using the crown ethers (entry 2 and 3) instead of the ammonium bromide (entry 1). In addition, isolated yields were improved as well as the selectivity towards the biaryl formation, DCH-18-C-6 being more efficient than 18-C-6. In order to prevent from the use of a toxic solvent, DMF could also be replaced by DMSO (entry 4 and 5).

The reaction was found to perform slightly faster with similar yields and this, even with 0.1 equiv. of DCH-18-C-6 (entry 5). However, moderate yields (i.e. 45%) were still obtained with this substrate, mainly due to the low selectivity of the reaction. In addition, the use of DMSO sometimes involved the degradation of the nitrile function into the corresponding amide therefore decreasing the efficiency of the catalytic system.

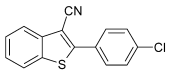
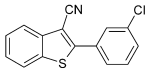
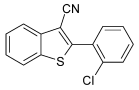
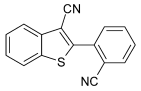
Some improvements were observed with 3-bromopyridine and 3-bromoquinoline (Table 2 entries 6–10). The replacement of the quaternary ammonium by DCH-18-C-6 dramatically enhanced the reaction rate (entries 7 and 10). However, in the case of 3-bromopyridine, DMF proved to be the best solvent giving a better reaction rate, selectivity and isolated yield (entries 7 and 8). At last, the use of DCH-18-C-6 instead of *n*-Bu_4NBr with 3-bromoquinoline (entries 9 and 10) afforded similar isolated yields but with a lower reaction time, a better selectivity and thus a straightforward purification.

The use of DCH-18-C-6 appeared to be particularly attractive with benzo[*b*]thiophene **2**, giving better yields with short reaction times. DMSO could be used as a solvent in replacement of DMF if the substrates did not degrade themselves under these conditions.

2.3. Effect of the substitutent at position 3

As for a comparison between benzo[*b*]thiophenes bearing different functional groups at the position 3, we used a catalytic system which involved the use of 5% of palladium diacetate, in the presence of tetra-*n*-butylammonium bromide and an excess of potassium carbonate. Indeed, benzo[*b*]thiophene-3-carboxaldehyde (commercially

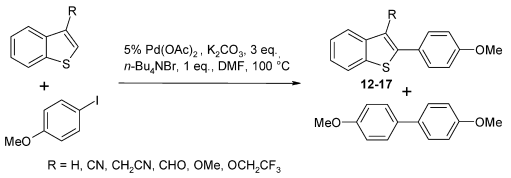
Table 1. Coupling studies on benzo[*b*]thiophene **2**. Influence of the additive

Entry	Product		Additive	Time (h)	Conversion (isolated yield) (%)	Selectivity Pdct/Ar–Ar
1		**5**	*n*-Bu_4NBr	1.5	98 (**69**)	10
			DCH-18-C-6	1.5	93 (**68**)	30
2		**6**	*n*-Bu_4NBr	2.5	99 (**72**)	5
			DCH-18-C-6	2	100 (**76**)	30
3		**7**	DCH-18-C-6	1.5	96 (**73**)	>50
4		**8**	*n*-Bu_4NBr	48	88 (**44**)	14
			DCH-18-C-6	2	100 (**63**)	>50

Typical procedure: see Section 4 procedures A and B.

available) was rapidly degradating in the presence of DCH-18-C-6, yielding non substituted benzo[*b*]thiophene by decarbonylation, hence the use of the ammonium salt. The coupling with 4-iodoanisole was then performed on 6 substituted benzo[*b*]thiophenes (Scheme 3, Table 4).

Unexpectedly, only benzo[*b*]thiophenes bearing either a mesomeric donating (OCH_3, OCH_2CF_3) or withdrawing (CHO, CN) group gave significant results in an acceptable reaction time (1–2 days). Non-substituted benzo[*b*]thiophene (entry 1) and the 3-acetonitrile one both showed a low



Scheme 3.

conversion and a poor selectivity towards the biaryl by-product (Table 3).

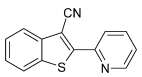
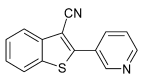
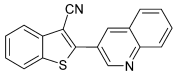
It was therefore reasonable to assume that an activation of the C2–C3 double bond was required and may enhance the reactivity of the benzo[*b*]thiophene in different parts of the catalytic cycle (see Section 2.6 for mechanistic considerations).

2.4. Effect of the nature of the halide

It is generally admitted for the Heck[32] and the Ullmann[30] reactions that the reactivity of the halide was the following: I>Br≫Cl≫F. As in the case of compounds **5**, **6**, **7** (Table 1) only a few traces of the product, where a substitution of the chlorine occurred, were detected by GC/MS, we reckoned that aryl chlorides were not reactive enough in our conditions.

We therefore compared the difference of reactivity of two

Table 2. Coupling studies on benzo[*b*]thiophene **2**. Influence of the additive and the solvent

Entry	Product		Additive	Solvent	Time (h)	Conversion (isolated yield) (%)	Selectivity Pdct/Ar–Ar
1		**9**	*n*-Bu_4NBr	DMF	96	56 (**27**)	0.6
2			18-C-6	DMF	20	87 (**35**)	2
3			DCH-18-C-6	DMF	20	89 (**44**)	2
4			DCH-18-C-6	DMSO	17	100 (**47**)	3
5			DCH-18-C-6[(a)]	DMSO	15	98 (**46**)	2
6		**10**	*n*-Bu_4NBr	DMF	120	98 (**41**)	>50
7			DCH-18-C-6	DMF	3	92 (**57**)	>50
8			DCH-18-C-6[(a)]	DMSO	15	96 (**52**)	20
9		**11**	*n*-Bu_4NBr	DMF	72	100 (**67**)	5
10			DCH-18-C-6	DMF	7	95 (**67**)	>50

Typical procedure: see Section 4 procedures A, B and C. (a) DCH-18-C-6=0.1 equiv.

Table 3. Effect of the substitutent at position 3

Entry	R	Pdct	Time (h)	Conversion (isolated yield)	Selectivity Pdct/Ar–Ar
1	H	**12**	48	15	0.6
2	CN	**13**	20	86 (**66**)	3.5
3	CH_2CN	**14**	48	12	1.2
4	CHO	**15**	24	82 (**50**)	2.8
5	OCH_3	**16**	28	95 (**61**)	3.5
6	OCH_2CF_3	**17**	48	98 (**66**)	11

aryl bromides with their corresponding iodides in the presence of benzo[*b*]thiophene-3-carboxaldehyde under the conditions cited above on Scheme 3 (Table 4). Unexpectedly, aryl bromides were found to react faster and more selectively than their iodine analogues. As a consequence, isolated yields were also much better, partly due to the ease of the separation. Indeed, with aryl iodides, the palladium specie underwent a rapid oxidative addition. Then we assumed that a second oxidative addition of Ar-I occurred, preventing the benzo[*b*]thiophene to react with the Ar-Pd-X specie. Thus the major product of the reaction was the biaryl compound and not the desired 2-arylbenzo[*b*]thiophene.

Aryl bromides were therefore employed rather than their iodides analogues and also due to their better availability and cheaper cost.

2.5. Coupling studies on benzo[*b*]thiophene-3-carboxaldehyde

Benzo[*b*]thiophene-3-carboxaldehyde was thus coupled with various aryl bromides with the conditions cited above on Scheme 3. Products of arylation were formed in acceptable reaction times (3–48 h) with a good selectivity (Table 5).

It was remarkable that isolated yields were not affected by the steric hindrance of cyano and nitro groups at *ortho* position in spite of longer reaction times than their *para* substituted analogues (entries 1–3). We also noticed that the nature of the substitutent on the aryl had almost no effect, the coupling being as efficient with electron-donating groups such as OMe (Table 4, entry 1) as with electron-withdrawing groups such as CN or NO_2 (Table 5 entries 1–3). However, the purification of compound **21** (entry 3) proved to be tedious hence yielding lower quantities of the desired compound. Finally, although the reaction time was longer than with other substrates, a quite good yield was obtained with 3-bromoquinoline (entry 5) with the same observed selectivity as with benzo[*b*]thiophene-3-carbonitrile (Table 2, entry 9).

2.6. Coupling studies on electron-rich benzo[*b*]thiophenes 3 and 4

We have already described[21] the syntheses of some 2-arylbenzo[*b*]thiophenes derived from the 3-methoxy substituted compound **3** (see entry 1 and 2 of Table 6 as examples). The coupling reaction was carried out at 100 °C as higher temperatures did not give better results. It was performed on **3** with other aryl halides, such as 2-bromotoluene (entries 3–4) and 3-bromoquinoline (entry 5). Similarly as observed with benzo[*b*]thiophene-3-carbonitrile, the use of DCH-18-C-6 in replacement of the ammonium bromide dramatically decreased the reaction time and, in parallel, improved the yields from 42 to 75%. Good yield and selectivity were also obtained with 3-bromoquinoline when using DCH-18-C-6 (entry 5).

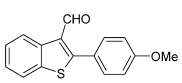
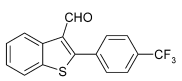
Compound **4**, 3-(2,2,2-trifluoroethoxy)benzo[*b*]-thiophene also reacted rapidly with excellent selectivities and good yields (entries 6 and 7). The *ortho*-substituted bromobenzonitrile even gave the coupled compound **29** within only 45 min (entry 7). However, it was noticed for electron-rich benzo[*b*]thiophenes that the conversion often stopped before being complete (entries 2, 3, 5 and 6). Indeed, the catalytic system was apparently less stable than with electron-poor benzo[*b*]thiophenes, as traces of palladium 'black' were observed after only a few hours. Therefore, we assumed that the catalytic cycle was different depending on the nature of the benzo[*b*]thiophene.

2.7. Catalytic cycle

It is noteworthy to outline that no conversion was observed with the benzo[*b*]thiophene-2-carbonitrile (synthesised via the 2-iodobenzo[*b*]thiophene according to the method described by Gaertner[33]). We reckon that a preliminary complexation of the palladium by the sulfur atom may lead the organometallic complex close to the position 2. In addition, the sulfur atom would probably stabilise a possible positive charge at position 2.

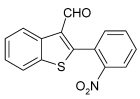
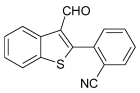
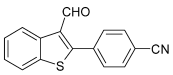
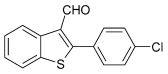
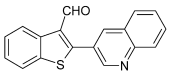
Considering the catalytic scheme generally admitted for the Heck reaction,[32] a $Pd^{(0)}$ complex undergoes an oxidative addition by the aryl halide. The complex may be formed in situ from several oxidised palladium species, the most

Table 4. Influence of the nature of the halide on the coupling

Entry	Product		Halide	Time (h)	Conversion (isolated yield) (%)	Selectivity Pdct/Ar–Ar
1		**15**	I	24	82 (**50**)	2.8
			Br	4	99 (**64**)	9
2		**18**	I	16	53 (**21**)	0.5
			Br	3	99 (**70**)	10

Typical procedure: see Section 4 procedure A.

Table 5. Coupling studies on benzo[*b*]thiophene-3-carboxaldehyde

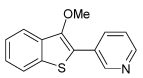
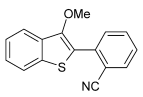
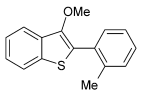
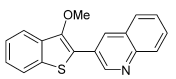
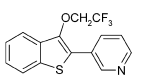
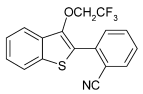
Entry	Product		Time (h)	Conversion and (isolated yield) (%)	Selectivity Pdct/Ar–Ar
1		**19**	18	99 (**56**)	7
2		**20**	20	99 (**54**)	18
3		**21**	3	95 (**41**)	7
4		**22**	5	98 (**58**)	8
5		**23**	48	86 (**52**)	5

Typical procedure: see Section 4 procedure A.

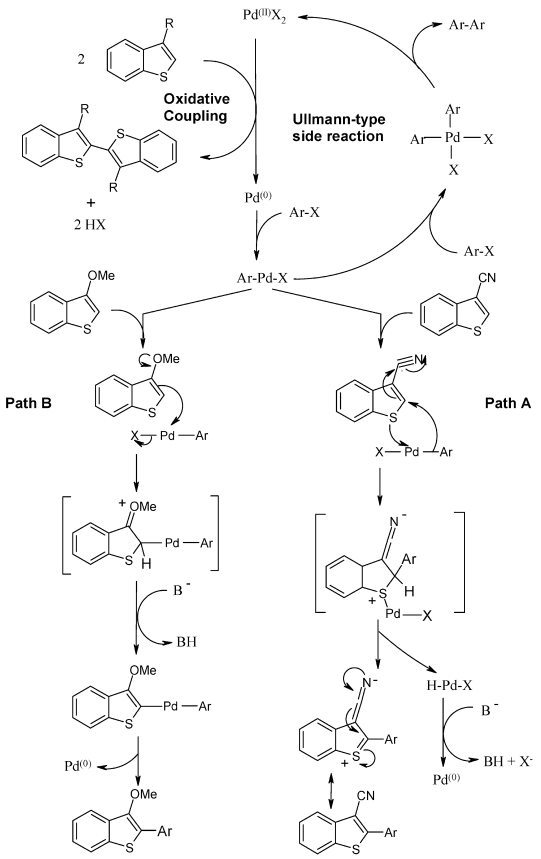
occurring one being $Pd(OAc)_2/PPh_3$.[20] In our case, a phosphine free system was used. Recently, Yao et al. proposed a mechanism of the Heck reaction for a phosphine free system based on palladium diacetate and K_3PO_4.[34] However, this mechanism could not be generalised to our system as their cycle made no difference on the nature of the olefin and therefore could not explain the lack of reactivity observed with benzo[*b*]thiophene and benzo[*b*]thiophene-3-acetonitrile (Table 3, entries 1 and 3). In addition, as in each reaction little quantities of benzo[*b*]thiophene dimer were isolated, we assumed that the reducing agent was the substrate itself, hence the gap between the conversion and the isolated yield. Indeed, Itahara[35] used palladium diacetate for direct aromatic arylation, yielding biaryls and palladium zero-valent. Thus it was noticed that, for most of the substrates, the better the selectivity between the main catalytic cycle and the Ullmann side reaction, the better the isolated yield. Indeed, the Ullmann path[16] generated some $Pd^{(II)}$ which should then be reduced by the substrate, hence lowering the yield.

It is reasonable to assume that there were two different mechanisms depending on the nature of the R group at position 3. For instance, Sharp et al. proposed[36] two different paths about the arylation at positions 2 or 5 of 3-carboalkoxy furan and thiophen. Similarly, we suppose that, in the case of R being a withdrawing group, the Ar-Pd-X specie would undergo a preliminary complexation from

Table 6. Coupling studies on benzo[*b*]thiophenes **3** and **4**

Entry	Substrate	Procedure	Product		Time (h)	Conversion and (isolated yield) (%)	Selectivity Pdct/Ar–Ar
1	**3**	A		**24**	25	95 (**66**)	>50
2	**3**	A		**25**	28	92 (**69**)	25
3	**3**	A		**26**	24	71 (**42**)	>50
4		B			4	97 (**75**)	>50
5	**3**	B		**27**	8	93 (**62**)	20
6	**4**	B		**28**	6	91 (**59**)	>50
7	**4**	B		**29**	0.75	99 (**76**)	>50

Typical procedure: see Section 4 procedures A and B.



Scheme 4.

the sulfur atom, followed by an insertion of the aryl at position 2. The resulting complex would then undergo a β-H elimination to yield the desired 2-arylbenzo[*b*]thiophene and a H-Pd-X specie which is then regenerated into $Pd^{(0)}$ by the base (Scheme 4, path A).

In the case of R being a donating group, the mechanism is analogous to the one recently proposed by Miura.[37] The electron-rich benzo[*b*]thiophene would first undergo an addition on the Ar-Pd-X specie. Then the base would eliminate the proton at position 2, hence regenerating the C2–C3 double bond. Finally, a reductive elimination would yield the desired compound and regenerate the catalyst (Scheme 4, path B).

3. Conclusion

In conclusion, we have shown that $Pd(OAc)_2$, in combination with K_2CO_3 and DCH-18-C-6 in either DMF or DMSO can be an efficient system for direct access to 2-arylbenzo[*b*]thiophenes. The reaction performed with both electron donating and electron withdrawing substitutents on aryl bromides in the absence of any supplementary stabilising ligands such as phosphines. In addition, although only benzo[*b*]thiophenes bearing an electron-withdrawing group or an electron-donating group at position 3 reacted, this system provided new interesting structures which diversity will constitute a pool of building blocks for a library of new drugs.

4. Experimental

4.1. General

The experimental details for the synthesis and the physical chemical data for compounds **6**, **13**, **24** and **25** have already been described in Ref. 21. Compound **16** has been described in Ref. 10.

Reactants and solvents have been supplied by Acros, Aldrich, Alfa Aesar, Fluka and Lancaster. Tlcs were performed with Merck 60 F_{254} silica gel plates. Flash chromatographies were performed with Merck Si 60 (40–63 μm) silica. Gas chromatographies were performed with Shimadzu GC-14A models with an apolar column and a flame ionisation detector and with the following programming: 100 °C (1 min) then +10 °C/min then 300 °C (1 min). Mass spectra were performed with a GC/MS FISONS INSTRUMENT MD 800 with the same temperature program as described above. NMR spectra were performed on either a Bruker AMX 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or a Bruker DPX 500, 500 MHz. Elemental analyses were made by the 'Service Central d'Analyse du CNRS' (Solaize, France). Melting points were measured on a Köfler bench.

4.1.1. 3-Bromo-benzo[*b*]thiophene 1. To a solution of benzo[*b*]thiophene (10 g; 74.5 mmol) in chloroform (75 mL) and acetic acid (75 mL), was added stepwise *N*-bromosuccinimide (16.6 g; 93.1 mmol) for 4 h at 0 °C and then allowed to stir at room temperature for 24 h. Then chloroform (30 mL) was added and the resulting mixture was successively washed with a saturated sodium thiosulfate solution (200 mL), a saturated sodium carbonate solution (200 mL) and water (150 mL). The extracted organic layer was then dried over $MgSO_4$, filtered and evaporated. The resulting red liquid was then filtered of a pad of silica, eluting with cyclohexane to afford **1** as a yellow oil (15.87 g, 100%); δ_H (300 MHz, $CDCl_3$) 7.43 (ddd, 1H, *J*=1.5, 7.4, 8.1 Hz), 7.45 (s, 1H), 7.49 (ddd, 1H, *J*=1.1, 7.4, 7.7 Hz), 7.85 (m, 2H) ppm; *m*/*z* 214 (100), 212 (90), 133 (50), 89 (70).

4.1.2. Benzo[*b*]thiophene-3-carbonitrile 2. A solution of 3-bromobenzo[*b*]thiophene **1** (15 g; 70.4 mmol), copper cyanide (7.7 g; 84 mmol) in dry dimethylacetamide (100 mL) was heated under reflux for 3 days under argon atmosphere. The mixture was diluted with ethylene diamine (35 mL) and water (70 mL) and extracted with dichloromethane (6×100 mL). The organic phase was successively washed with a 10% solution of sodium cyanide (2×100 mL), brine (100 mL) and water (100 mL), then dried over $MgSO_4$, filtered and evaporated. The brown crude mixture was filtered over a short pad of silica, eluting with cyclohexane, to afford **2** as a white crystalline powder (5.5 g, 78%); mp 71–72 °C; R_f 0.3 (silica, cyclohexane/AcOEt 90:10); δ_H (300 MHz, $CDCl_3$) 7.48 (ddd, 1H, *J*=1.1, 7.0, 7.0 Hz), 7.53 (ddd, 1H, *J*=1.1, 7.0, 7.0 Hz), 7.91 (ddd, 1H, *J*=0.7, 1.1, 7.0 Hz), 8.00 (ddd, 1H, *J*=0.7, 1.1, 7.0 Hz), 8.14 (s, 1H); δ_C (75 MHz, $CDCl_3$) 107.2 (C), 114.4 (CN), 122.6 (CH), 122.9 (CH), 126.1 (CH), 126.3 (CH), 137.3 (C), 137.6 (CH), 138.6 (C) ppm; *m*/*z* 159 (100), 132 (10).

4.1.3. 3-Methoxy-benzo[*b*]thiophene 3. To a solution of **1** (4.45 g; 20.9 mmol) in methanol (40 mL), was added sodium methoxyde (11.26 g; 209 mmol), copper oxide (835 mg; 10.5 mmol), KI (50 mg; 0.24 mmol), CuI (80 mg; 0.4 mmol) and DMF (50 mL) and then was refluxed for 24 h. The mixture was hydrolysed by water (40 mL), filtered and then DCM (70 mL) was added. The mixture was successively washed with a saturated solution of ammonium chloride (100 mL), a saturated sodium thiosulfate solution (2×100 mL) and water (100 mL). The extracted organic layer was then dried over $MgSO_4$, filtered and evaporated. The resulting red liquid was then purified by flash chromatography, eluting with cyclohexane to afford **3** as a pale yellow oil (3.48 g, 100%); R_f 0.5 (silica, cyclohexane/AcOEt 95:5); δ_H (300 MHz, $CDCl_3$) 3.96 (s, 3H, OCH_3), 6.28 (s, 1H), 7.33–7.38 (m, 2H), 7.74–7.80 (m, 2H); δ_C (75 MHz, $CDCl_3$) 57.6 (CH_3), 95.9 (CH), 121.3 (CH), 123.2 (CH), 124.1 (CH), 125.6 (CH), 132.5 (C), 138.2 (C), 152.3 (C) ppm; *m*/*z* 164 (70), 149 (100), 121 (60).

4.1.4. 3-(2,2,2-Trifluoroethoxy)benzo[*b*]thiophene 4. In a round bottomed flask containing NaH (505 mg, 21 mmol) was added stepwise, at 0 °C under argon, a solution of 2,2,2-trifluoroethanol (1.5 mL, 21 mmol) in anhydrous DMF (4 mL). After stirring for 20 min, 3-bromobenzo[*b*]thiophene **1** (3.19 g, 15 mmol) and CuI (143 mg, 0.75 mmol) were added. The resulting mixture was refluxed for 17 h and then cooled. Dichloromethane (40 mL) was added, the mixture was filtered of a short pad of celite and then successively washed with a saturated solution of ammonium chloride (30 mL) and water (30 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was then purified by flash chromatography (cyclohexane) to afford **4** as a yellow oil (1.73 g, 54%); R_f 0.1 (silica, cyclohexane); found C 52.25, H 2.84%, $C_{10}H_7F_3OS$ requires C 51.72, H 3.04%; δ_H (300 MHz, $CDCl_3$) 4.49 (q, CH_2, *J*=8.1 Hz), 6.39 (s, 1H), 7.42 (m, 2H), 7.78 (m, 1H), 7.88 (m, 1H); δ_C (75 MHz, $CDCl_3$) 67.7 (q, CH_2, *J*=36 Hz), 98.8 (CH), 121.4 (CH), 123.3 (CH), 124.6 (CH), 126.1 (CH), 131.8 (C), 138.1 (C), 149.5 (C); δ_F (188 MHz, $CDCl_3$) −74.3 (t, 3F, *J*=8.1 Hz) ppm; *m*/*z* 234 (10), 232 (90), 151 (20), 149 (100).

4.2. Typical procedure A

A suspension of potassium carbonate (3.75 mmol), tetra-*n*-butylammonium bromide (1.25 mmol), substituted benzothiophene (1.25 mmol) and aryl halide (1.25 mmol) in *N*,*N*-dimethylformamide (1.25 mL) was stirred under argon at the indicated temperature for 5 min. Palladium diacetate (0.0625 mmol) was then added and the resulting mixture was allowed to stir for the time indicated, adding stepwise aryl halide (0.375 by 0.375 mmol) until no change of the chemical yield (determined by G.C). After cooling to room temperature, the mixture was filtered over Celite®, rinsed with dichloromethane (10 mL) and then successively washed with brine (10 mL), a saturated sodium thiosulfate solution (10 mL) and water (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to give a brown residue. The latter was then purified by flash column chromatography (silica, cyclohexane/AcOEt) to afford the pure desired compound.

4.3. Typical procedure B

Same as procedure A but dicyclohexyl-18-crown-6 (1.25 mmol) was used instead of tetra-*n*-butylammonium bromide.

4.4. Typical procedure C

Same as procedure A but dicyclohexyl-18-crown-6 (0.13 mmol) was used instead of tetra-*n*-butylammonium bromide and the reaction was performed in DMSO (1.25 mL) instead of DMF.

4.4.1. 2-(4′-Chlorobenzyl)-benzo[*b*]thiophene-3-carbonitrile 5. Prepared according to procedure B. Isolated yield: 68%; white solid; mp 135–136 °C; R_f 0.20 (silica, cyclohexane/AcOEt 95:5); found C 66.49, H 3.06, N 5.14, S 12.00, Cl 13.00%, $C_{15}H_8ClNS$ requires C 66.79, H 2.99, N 5.19, S 11.89, Cl 13.14%; δ_H (500 MHz, $CDCl_3$) 7.47 (ddd, 1H, *J*=1.0, 7.4, 8.2 Hz), 7.50 (d, 2H, *J*=8.7 Hz), 7.54 (ddd, 1H, *J*=1.0, 7.4, 8.1 Hz), 7.83 (d, 2H, *J*=8.7 Hz), 7.85 (d, 1H, *J*=8.2 Hz), 7.97 (d, 1H, *J*=8.1 Hz); δ_C (75 MHz, $CDCl_3$) 102.9 (C), 115.3 (CN), 122.8 (CH), 123.1 (CH), 126.7 (CH), 126.8 (CH), 129.8 (2CH), 130.0 (2CH), 130.3 (C), 137.1 (C), 137.8 (C), 139.5 (C), 153.8 (C) ppm; *m*/*z* 271 (30), 269 (100), 233 (20).

4.4.2. 2-(2′-Chlorobenzyl)-benzo[*b*]thiophene-3-carbonitrile 7. Prepared according to procedure B. Isolated yield: 73%; pale yellow solid; m.p. 133–134 °C; R_f 0.15 (silica, cyclohexane/AcOEt 97:3); found C 67.06, H 2.91, N 5.20%, $C_{15}H_8ClNS$ requires C 66.79, H 2.99, N 5.19%; δ_H (500 MHz, $CDCl_3$) 7.41 (ddd, 1H, *J*=1.0, 7.5, 7.8 Hz), 7.46 (ddd, 1H, *J*=1.9, 7.5, 8.0 Hz), 7.51 (ddd, 1H, *J*=1.0, 7.2, 7.9 Hz), 7.54–7.60 (m, 3H), 7.89 (d, 1H, *J*=7.8 Hz), 8.01 (d, 1H, *J*=8.0 Hz); δ_C (75 MHz, $CDCl_3$) 107.3 (C), 114.5 (C), 122.8 (CH), 123.2 (CH), 126.5 (CH), 126.8 (CH), 127.6 (CH), 130.6 (C), 130.9 (CH), 131.9 (CH), 132.5 (CH), 134.0 (C), 138.2 (C), 139.1 (C), 152.1 (C) ppm; *m*/*z* 271 (10), 269 (100), 233 (70), 189 (80).

4.4.3. 2-(2′-Benzonitrile)-benzo[*b*]thiophene-3-carbonitrile 8. Prepared according to procedure B. Isolated yield: 63%; pale yellow solid; mp 191–193 °C; R_f 0.15 (silica, cyclohexane/AcOEt 95:5); found C 73.29, H 3.09, N 10.48%, $C_{16}H_8N_2S$ requires C 73.82, H 3.10, N 10.76%; δ_H (300 MHz, $CDCl_3$) 7.54 (ddd, 1H, *J*=1.3, 7.2, 7.3 Hz), 7.60 (ddd, 1H, *J*=1.3, 7.3, 7.5 Hz), 7.66 (m, 1H), 7.77 (m, 2H), 7.88 (d, 1H, *J*=8.86 Hz), 7.92 (d, 1H, *J*=7.5 Hz), 8.03 (d, 1H, *J*=7.2 Hz); δ_C (75 MHz, $CDCl_3$) 107.41 (C), 113.25 (C), 114.21 (CN), 117.56 (CN), 122.96 (CH), 123.52 (CH), 126.91 (CH), 127.33 (CH), 130.90 (CH), 131.69 (CH), 133.62 (CH), 134.63 (CH), 134.94 (C), 138.38 (C), 139.07 (C), 150.09 (C) ppm; *m*/*z* 260 (100), 233 (10).

4.4.4. 2-(2′-Pyridine)-benzo[*b*]thiophene-3-carbonitrile 9. Prepared according to procedure C. Isolated yield: 46%; pale yellow solid; mp 170–171 °C; R_f 0.1 (silica, cyclohexane/AcOEt 95:5); found C 70.95, H 3.04, N 11.74%, $C_{14}H_8N_2S$ requires C 71.16, H 3.41, N 11.86%; δ_H (300 MHz, $CDCl_3$) 7.36 (ddd, 1H, *J*=0.9, 4.9, 7.7 Hz), 7.47 (ddd, 1H, *J*=1.3, 7.2, 7.2 Hz), 7.52 (ddd, 1H, *J*=1.3, 7.2, 7.2 Hz), 7.85 (dd, 1H, *J*=1.9, 8.1 Hz), 7.88 (dd, 1H,

J=1.3, 7.2 Hz), 7.97 (dd, 1H, J=1.3, 7.2 Hz), 8.40 (ddd, 1H, J=0.9, 8.1, 8.1 Hz), 8.70 (ddd, 1H, J=0.9, 1.5, 4.7 Hz); δ_C (75 MHz, $CDCl_3$) 102.3 (C), 115.6 (CN), 121.6 (CH), 122.9 (CH), 123.0 (CH), 125.1 (CH), 126.5 (CH), 127.1 (CH), 137.7 (C), 138.7 (C), 139.8 (C), 150.1 (CH), 150.4 (C), 155.4 (C) ppm; *m/z* 236 (100), 209 (10), 78 (10).

4.4.5. 2-(3′-Pyridine)-benzo[*b*]thiophene-3-carbonitrile 10. Prepared according to procedure C. Isolated yield: 52%; yellow solid; mp 150–152 °C; R_f 0.15 (silica, cyclohexane/AcOEt 95:5); found C 71.28, H 3.54, N 11.71, S 13.69%, $C_{14}H_8N_2S$ requires C 71.16, H 3.41, N 11.86, S 13.57%; δ_H (300 MHz, $CDCl_3$) 7.43 (ddd, 1H, J=1.3, 7.3, 8.1 Hz), 7.45 (dd, 1H, J=4.0, 8.1 Hz), 7.52 (ddd, 1H, J=1.0, 7.3, 7.5 Hz), 7.84 (d, 1H, J=7.5 Hz), 7.94 (dd, 1H, J=1.0, 8.1 Hz), 8.21 (ddd, 1H, J=1.6, 1.6, 8.1 Hz), 8.73 (d, 1H, J=4.0 Hz), 9.06 (d, 1H, J=1.6 Hz); δ_C (75 MHz, $CDCl_3$) 103.9 (C), 114.9 (CN), 122.9 (CH), 123.2 (CH), 124.3 (CH), 126.8 (CH), 127.1 (CH), 128.2 (C), 135.6 (CH), 138.0 (C), 139.2 (C), 149.2 (CH), 151.0 (C), 151.6 (CH) ppm; *m/z* 236 (100).

4.4.6. 2-(4′-Anisyl)-benzo[*b*]thiophene-3-carboxaldehyde 15. Prepared according to procedure A. Isolated yield: 64%; pale yellow solid; mp 75–76 °C; R_f 0.4 (silica, cyclohexane/AcOEt 95:5); found C 71.34, H 4.39, O 11.88, S 11.74%, $C_{16}H_{12}O_2S$ requires C 71.62, H 4.51, O 11.93, S 11.95%; δ_H (300 MHz, $CDCl_3$) 3.87 (s, 3H, OCH_3), 6.99 (d, 2H, J=8.8 Hz), 7.39 (ddd, 1H, J=0.6, 7.4, 8.1 Hz), 7.47 (m, 1H), 7.51 (d, 2H, J=8.8 Hz), 7.79 (d, 1H, J=7.9 Hz), 8.76 (dd, 1H, J=0.7, 7.4 Hz), 10.05 (s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 55.9 (CH_3), 114.8 (2CH), 122.0 (CH), 124.2 (C), 125.4 (CH), 126.0 (CH), 126.6 (CH), 130.0 (C), 132.3 (2CH), 137.7 (C), 138.0 (C), 161.4 (C), 161.6 (C), 187.2 (CHO) ppm; *m/z* 268 (100), 267 (70), 237 (30).

4.4.7. 2-(4′-Anisyl)-3-methoxybenzo[*b*]thiophene 16. Prepared according to procedure A. Isolated yield 61%; pink solid; mp 62–64 °C; R_f 0.35 (silica, cyclohexane/AcOEt 95:5); δ_H (300 MHz, $CDCl_3$) 3.75 (s, CH_3), 3.76 (s, CH_3), 6.99 (d, 2H, J=8.9 Hz), 7.34 (ddd, 1H, J=1.3, 7.3, 7.3 Hz), 7.40 (ddd, 1H, J=1.2, 7.3, 7.3 Hz), 7.72–7.78 (m, 2H), 7.81 (d, 2H, J=8.9 Hz); δ_C (75 MHz, $CDCl_3$) 55.7 (CH_3), 61.1 (CH_3), 114.6 (2CH), 121.1 (CH), 123.1 (CH), 124.7 (CH), 125.1 (CH), 125.9 (C), 127.1 (C), 129.6 (2CH), 135.3 (C), 135.7 (C), 146.8 (C), 159.7 (C) ppm; *m/z* 270 (70), 255 (100), 227 (80), 212 (70), 184 (60).

4.4.8. 2-(4′-Anisyl)-3-(2,2,2-trifluoroethoxy)benzo[*b*]-thiophene 17. Prepared according to procedure A. Isolated yield 66%; pink crystals; mp 78–80 °C; R_f 0.10 (silica, cyclohexane); found C 60.17, H 3.96%, $C_{17}H_{13}F_3O_2S$ requires C 60.35, H 3.87%; δ_H (300 MHz, $CDCl_3$) 3.88 (s, OCH_3), 4.23 (q, CH_2, J=8.4 Hz), 7.01 (d, 2H, J=8.9 Hz), 7.36 (ddd, 1H, J=1.4, 7.5, 7.9 Hz), 7.42 (ddd, 1H, J=1.3, 7.4, 7.5 Hz), 7.74 (d, 2H, J=8.9 Hz), 7.76 (m, 2H); δ_C (75 MHz, $CDCl_3$) 55.7 (CH_3), 69.4 (q, CH_2, J=35.0 Hz), 114.9 (2CH), 116.3 (C), 120.8 (CH), 123.1 (CH), 124.7 (C), 125.1 (CH), 125.5 (CH), 129.9 (2CH), 134.4 (C), 135.6 (C), 143.8 (C), 160.2 (C); δ_F (282 MHz, $CDCl_3$) −74.9 (t, 3F, J=8.4 Hz) ppm; *m/z* 340 (30), 338 (60), 255 (100).

4.4.9. 2-(4′-Benzotrifluoride)-benzo[*b*]thiophene-3-carboxaldehyde 18. Prepared according to procedure A. Isolated yield: 70%; pale brown solid; mp 96–98 °C; R_f 0.6 (silica, cyclohexane/AcOEt 95:5); found C 62.64, H 2.76, F 18.81%, $C_{16}H_9F_3OS$ requires C 62.74, H 2.96, F 18.61%; δ_H (300 MHz, $CDCl_3$) 7.48 (ddd, 1H, J=1.2, 7.4, 8.2 Hz), 7.55 (ddd, 1H, J=1.0, 7.4, 8.2 Hz), 7.72 (d, 2H, J=8.3 Hz), 7.80 (d, 2H, J=8.3 Hz), 7.87 (d, 1H, J=7.4 Hz), 8.80 (dd, 1H, J=1.2, 8.0 Hz), 10.05 (s, 1H); δ_C (75 MHz, $CDCl_3$) 120.8 (CH), 122.8 (q, CF_3, J=272.8 Hz), 124.4 (CH), 124.9 (q, 2CH, J=3.7 Hz), 125.4 (CH), 125.7 (CH), 129.9 (C), 130.0 (2CH), 131.0 (q, C, J=32.7 Hz), 134.3 (C), 136.0 (C), 137.2 (C), 157.0 (C), 185.0 (CHO) ppm; *m/z* 306 (80), 305 (100), 237 (60), 208 (50), 160 (20).

4.4.10. 2-(2′-Nitrophenyl)-benzo[*b*]thiophene-3-carboxaldehyde 19. Prepared according to procedure A. Isolated yield: 56%; yellow solid; mp 155–156 °C; R_f 0.1 (silica, cyclohexane/AcOEt 95:5); found C 63.72, H 3.20, N 5.01, O 17.12%, $C_{15}H_9NO_3S$ requires C 63.59, H 3.20, N 4.94, O 16.94%; δ_H (300 MHz, $CDCl_3$) 7.48 (ddd, 1H, J=1.4, 7.2, 8.0 Hz), 7.55 (ddd, 1H, J=1.4, 7.2, 8.0 Hz), 7.61 (dd, 1H, J=1.5, 6.2 Hz), 7.70 (ddd, 1H, J=1.5, 6.2, 7.5 Hz), 7.75 (ddd, 1H, J=1.5, 6.7, 7.5 Hz), 7.86 (dd, 1H, J=1.5, 6.7 Hz), 8.16 (dd, 1H, J=1.4, 7.2 Hz), 8.71 (dd, 1H, J=1.4, 7.2 Hz), 9.86 (s, 1H); δ_C (75 MHz, $CDCl_3$) 121.9 (CH), 125.0 (CH), 125.1 (CH), 126.4 (CH), 126.5 (C), 126.6 (CH), 131.1 (CH), 131.9 (C), 132.9 (CH), 133.7 (CH), 136.2 (C), 138.8 (C), 146.6 (C), 153.9 (C), 185.0 (CHO) ppm; *m/z* 283 (40), 163 (100), 119 (80), 93 (50).

4.4.11. 2-(2′-Benzonitrile)-benzo[*b*]thiophene-3-carboxaldehyde 20. Prepared according to procedure A. Isolated yield: 54%; orange crystals; mp 172–174 °C; R_f 0.1 (silica, cyclohexane/AcOEt 95:5); found C 72.97, H 3.54, N 5.50%, $C_{16}H_9NOS$ requires C 72.98, H 3.45, N 5.32%; δ_H (500 MHz, $CDCl_3$) 7.53 (ddd, 1H, J=1.3, 7.6, 7.6 Hz), 7.59 (ddd, 1H, J=1.0, 7.6, 7.9 Hz), 7.68 (ddd, 1H, J=1.2, 7.6, 8.2 Hz), 7.69 (d, 1H, J=7.9 Hz), 7.77 (ddd, 1H, J=1.3, 7.6, 7.9 Hz), 7.89 (dd, 1H, J=1.3, 7.9 Hz), 7.91 (d, 1H, J=8.2 Hz), 8.71 (dd, 1H, J=1.0, 7.6 Hz), 9.91 (s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 114.4 (C), 117.4 (C), 122.2 (CH), 125.8 (CH), 126.9 (CH), 127.0 (CH), 130.7 (CH), 132.6 (CH), 133.2 (CH), 134.0 (CH), 135.4 (C), 136.7 (C), 139.1 (C), 154.3 (C), 185.4 (CHO) ppm; *m/z* 262 (80), 235 (100), 190 (90).

4.4.12. 2-(4′-Benzonitrile)-benzo[*b*]thiophene-3-carboxaldehyde 21. Prepared according to procedure A. Isolated yield: 41%; pale green solid; mp 168–169 °C; R_f 0.1 (silica, cyclohexane/AcOEt 95:5); found C 72.67, H 3.45, N 5.31, O 6.43%, $C_{16}H_9NOS$ requires C 72.98, H 3.45, N 5.32, O 6.08%; δ_H (300 MHz, $CDCl_3$) 7.48 (ddd, 1H, J=1.0, 7.3, 8.1 Hz), 7.55 (ddd, 1H, J=1.1, 7.4, 8.1 Hz), 7.70 (d, 2H, J=7.5 Hz), 7.81 (d, 2H, J=7.5 Hz), 7.89 (dd, 1H, J=1.1, 7.3 Hz), 8.77 (dd, 1H, J=1.0, 7.4 Hz), 10.03 (s, 1H); δ_C (75 MHz, $CDCl_3$) 113.9 (C), 118.1 (C), 121.9 (CH), 125.5 (CH), 126.6 (C), 126.8 (C), 131.1 (C), 131.3 (2CH), 132.7 (2CH), 136.3 (C), 137.0 (C), 138.3 (C), 157.1 (C), 185.7 (CHO) ppm; *m/z* 263 (70), 262 (100), 235 (20), 190 (60).

4.4.13. 2-(4′-Chloro-phenyl)-benzo[*b*]thiophene-3-carboxaldehyde 22. Prepared according to procedure

A. Isolated yield: 58%; pale yellow solid; mp 96–98 °C; R_f 0.35 (silica, cyclohexane/AcOEt 97:3); found C 66.40, H 3.44, Cl 13.04%, $C_{15}H_9ClOS$ requires C 66.05, H 3.33, Cl 13.00%; δ_H (300 MHz, $CDCl_3$) 7.38–7.57 (m, 6H), 7.78 (ddd, 1H, J=0.8, 1.4, 7.5 Hz), 8.77 (ddd, 1H, J=0.8, 1.3, 7.5 Hz), 10.01 (s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 122.0 (CH), 125.6 (CH), 126.4 (CH), 126.8 (CH), 129.6 (2CH), 130.4 (C), 130.7 (C), 132.1 (2CH), 136.9 (C), 137.4 (C), 138.3 (C), 159.2 (C), 186.5 (CHO) ppm; *m/z* 271 (100), 243 (30), 163 (98).

4.4.14. 2-(3′-Quinolyl)-benzo[*b*]thiophene-3-carboxaldehyde 23. Prepared according to procedure A. Isolated yield: 52%; white solid; mp 179–180 °C; R_f 0.1 (silica, cyclohexane/AcOEt 95:5); found C 74.61, H 3.84, N 4.81%, $C_{18}H_{11}NOS$ requires C 74.72, H 3.83, N 4.84%; δ_H (500 MHz, $CDCl_3$) 7.49 (ddd, 1H, J=1.2, 7.9, 8.2 Hz), 7.56 (ddd, 1H, J=1.1, 8.1, 8.2 Hz), 7.67 (ddd, 1H, J=1.3, 7.0, 8.2 Hz), 7.84 (ddd, 1H, J=1.6, 7.0, 8.3 Hz), 7.89 (d, 1H, J=7.9 Hz), 7.93 (d, 1H, J=8.2 Hz), 8.22 (d, 1H, J=8.3 Hz), 8.39 (d, 1H, J=2.2 Hz), 8.83 (d, 1H, J=8.1 Hz), 9.16 (d, 1H, J=2.2 Hz), 10.12 (s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 122.1 (CH), 125.4 (C), 125.7 (CH), 126.7 (CH), 127.0 (CH), 127.4 (C), 128.4 (CH), 128.7 (CH), 130.0 (CH), 131.5 (CH), 131.6 (C), 137.4 (C), 138.1 (CH), 138.7 (C), 148.7 (C), 150.7 (CH), 156.5 (C), 186.2 (CHO) ppm; *m/z* 290 (10), 289 (100), 288 (90), 260 (30).

4.4.15. 2-(2′-Toluyl)-3-methoxybenzo[*b*]thiophene 26. Prepared according to procedure B. Isolated yield 75%; slightly yellow oil; R_f 0.6 (silica, cyclohexane/AcOEt 98:2); found C 75.27, H 5.55%, $C_{16}H_{14}OS$ requires C 75.56, H 5.55%; δ_H (500 MHz, $CDCl_3$) 2.40 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 7.27 (ddd, 1H, J=1.8, 7.3, 7.8 Hz), 7.33 (m, 1H), 7.35 (ddd, 1H, J=1.1, 7.8, 8.0 Hz), 7.39 (ddd, 1H, J=1.3, 7.3, 8.6 Hz), 7.43 (ddd, 1H, J=1.0, 7.3, 7.9 Hz), 7.49 (dd, 1H, J=1.1, 7.3 Hz), 7.77 (ddd, 1H, J=0.6, 1.0, 7.9 Hz), 7.83 (ddd, 1H, J=0.6, 1.3, 8.6 Hz); δ_C (75 MHz, $CDCl_3$) 20.8 (CH_3), 61.0 (OCH_3), 121.6 (CH), 122.6 (C), 122.9 (CH), 124.5 (CH), 125.3 (CH), 126.0 (CH), 129.1 (CH), 130.6 (CH), 131.8 (CH), 132.8 (C), 134.4 (C), 137.1 (C), 138.8 (C), 147.3 (C) ppm; *m/z* 254 (30), 239 (30), 221 (60), 211 (40), 178 (100).

4.4.16. 2-(3′-Quinolyl)-3-methoxybenzo[*b*]thiophene 27. Prepared according to procedure B. Isolated yield: 62%; orange-red solid; mp 70–71 °C; R_f 0.55 (silica, cyclohexane/AcOEt 95:5); found C 73.80, H 4.51, N 4.67%, $C_{18}H_{13}NOS$ requires C 74.20, H 4.50, N 4.81%; δ_H (500 MHz, $CDCl_3$) 3.94 (s, 3H, CH_3), 7.38 (dd, 1H, J=6.9, 7.3 Hz), 7.42 (dd, 1H, J=6.9, 7.8 Hz), 7.58 (dd, 1H, J=6.9, 7.8 Hz), 7.72 (dd, 1H, J=6.9, 8.2 Hz), 7.81 (d, 1H, J=7.8 Hz), 7.82 (d, 1H, J=7.3 Hz), 7.87 (d, 1H, J=7.8 Hz), 8.13 (d, 1H, J=8.2 Hz), 8.50 (d, 1H, J=2.1 Hz), 9.46 (d, 1H, J=2.1 Hz); δ_C (125 MHz, $CDCl_3$) 61.7 (CH_3), 121.7 (CH), 123.4 (CH), 123.7 (C), 125.0 (CH), 126.0 (CH), 126.9 (C), 127.6 (CH), 128.3 (C), 128.5 (CH), 129.6 (CH), 130.2 (CH), 134.2 (CH), 134.7 (C), 136.6 (C), 147.5 (C), 149.3 (C), 150.1 (CH) ppm; *m/z* 291 (95), 276 (100), 248 (70), 76 (70).

4.4.17. 2-(3′-Pyridyl)-3-(2,2,2-trifluoroethoxy)benzo[*b*]thiophene 28. Prepared according to procedure B. Isolated yield 59%; colourless oil; R_f 0.15 (silica, cyclohexane/AcOEt: 95/5); found C 58.27, H 3.18, N 4.51%, $C_{15}H_{10}F_3NOS$ requires C 58.25, H 3.26, N 4.53%; δ_H (500 MHz, $CDCl_3$) 4.29 (q, 2H, J=8.2 Hz), 7.41 (m, 2H), 7.45 (ddd, 1H, J=1.3, 7.5, 7.9 Hz), 7.78 (dd, 1H, J=1.5, 7.6 Hz), 7.80 (dd, 1H, J=1.3, 7.2 Hz), 8.13 (ddd, 1H, J=1.3, 1.6, 8.2 Hz), 8.61 (dd, 1H, J=1.3, 4.7 Hz), 9.01 (d, 1H, J=1.6 Hz); δ_C (75 MHz, $CDCl_3$) 70.0 (q, CH_2, J=35 Hz), 121.1 (CH), 121.6 (C), 123.4 (CH), 124.0 (C), 124.9 (C), 125.4 (CH), 126.3 (CH), 127.0 (q, CF_3, J=257 Hz), 133.5 (CH), 135.4 (CH), 136.3 (C), 145.7 (C), 149.2 (CH), 149.6 (CH); δ_F (282 MHz, $CDCl_3$) −74.74 (t, 3F, J=8.2 Hz) ppm; *m/z* 309 (40), 226 (100), 198 (80).

4.4.18. 2-(2′-Benzonitrile)-3-(2,2,2-trifluoroethoxy)benzo[*b*]thiophene 29. Prepared according to procedure B. Isolated yield 76%; colourless oil; R_f 0.3 (silica, cyclohexane/AcOEt: 95/5); found C 61.42, H 2.97, N 4.28%, $C_{17}H_{10}F_3NOS$ requires C 61.26, H 3.02, N 4.20%; δ_H (500 MHz, $CDCl_3$) 4.24 (q, 2H, J=8.2 Hz), 7.44 (ddd, 1H, J=1.6, 6.9, 7.0 Hz), 7.47 (ddd, 1H, J=1.5, 7.0, 7.2 Hz), 7.53 (ddd, 1H, J=2.5, 6.3, 7.9 Hz), 7.67–7.71 (m, 2H), 7.80–7.85 (m, 3H); δ_C (75 MHz, $CDCl_3$) 70.3 (q, CH_2, J=35 Hz), 113.7 (C), 118.2 (C), 121.6 (CH), 123.3 (CH), 125.4 (CH), 126.5 (CH), 129.4 (CH), 132.1 (CH), 132.8 (C), 133.2 (CH), 134.2 (CH), 135.6 (C), 137.3 (C), 146.7 (C), 149.9 (C); δ_F (282 MHz, $CDCl_3$) −75.10 (t, 3F, J=8.2 Hz) ppm; *m/z* 333 (60), 250 (100), 222 (70).

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