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Heck-type coupling of intramolecularly-generated thiopalladacycles with alkenes: One pot syntheses of 3-alkenylbenzo[*b*]thiophenes

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ABSTRACT

A method for stoichiometric functionalization of benzothiophene is developed by Heck-type coupling of alkenes with intramolecularly-generated thiopalladacycles obtained from palladium salts and *ortho*-thioanisole-substituted propargyl imines. The synthetic strategy for preparing structurally diverse 3-alkenylbenzo[*b*]thiophene is also extended to 3-alkenylbenzo[*b*]selenophenes.

1. Introduction

Substituted benzo[*b*]thiophenes have received great attention because their structural fragment displays a wide range of biological and physiological properties [1–4]. In particular, the 2,3-disubstituted benzothiophene structural framework constitutes a core unit of several pharmaceutical candidates and are in development of selective oestrogen receptor modulators (SERM) [5–7], tubulin-binding agents [8–10], modulators of multi-drug resistance [11], angiogenesis inhibitors [12–14], site-directed thrombin inhibitors [15,16], and anti-inflammatory agents [17,18]. Conventionally, the synthesis and functionalization of heteroaromatics is achieved by different types of cross-coupling reactions of a heterocycle bearing a metal-containing functionality (nucleophilic component) [19–21] or a halogen atom (electrophilic component) [1,2,10]. Friedel–Crafts-type alkylation/halogenation of heteroaromatics is also a well-established [22–24], however it is limited to electron-rich substrates only. The functionalization of heterocycles via the activation of unreactive C–H bonds also constitutes an alternative approach [25–28].

The cyclization of *ortho*-alkynyl anilines and *ortho*-alkynyl phenols in the presence of an organopalladium complex is a common method for the direct synthesis of functionalized indoles and benzofurans [29–36]. However, the use of transition metals, including palladium, in the synthesis of functionalized benzothiophenes from substituted *ortho*-thioanisoles is often restricted because of their incompatibility with sulphur-containing substrates [37–43]. Recently, the direct synthesis of functionalized benzo[*b*]thiophenes has been reported by gold-catalyzed intramolecular carbothiolation of alkynes [44]. Herein, we report a method for the functionalization of benzothiophene via Heck-type coupling of alkenes with intramolecularly-generated thiopalladacycles obtained from stoichiometric amount of palladium salts and *ortho*-thioanisole substituted propargyl imines. An important feature of the thiopalladacycles is, it provides useful information of intermediate Pd-vinyl species generated via intramolecular thiopalladation (Fig. 1, Type B) [45]. The palladium-catalyzed (cyclization) annulation of alkynes to heterocycles, such as indoles and benzofurans, proceed via an intramolecular pathway and the formation of a heterocyclic ring system realized through the generation of organopalladium intermediate species which is practically not isolated so far to the best of our knowledge (Fig. 1, Type A) [29–36].

2. Results and discussion

In view of the importance of substituted benzothiophenes as useful heterocyclic cores for drug and drug candidates in the development of new materials [46–49], we have extended our

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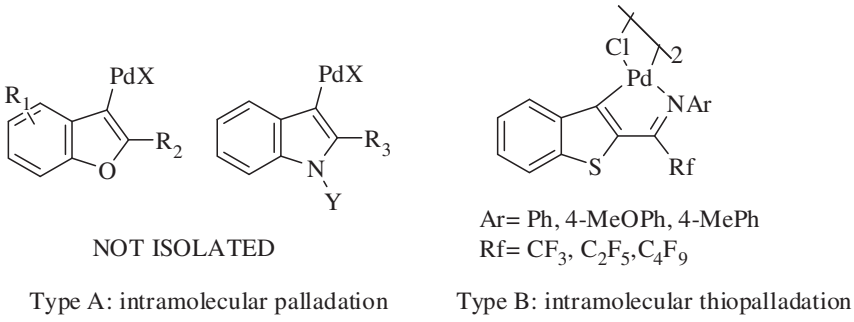


Fig. 1. Intramolecular palladation of alkynes.

on-going effort to the synthesis of 3-alkenylbenzo[*b*]thiophenes via the generation of benzothiophene-based palladacycles.

To extend the application of the thiopalladacycles in the synthesis of 3-alkenylbenzo[*b*]thiophene, thiopalladacycles were initially prepared by the reaction of propargyl imine bearing an *ortho*-thioanisole with a THF solution of $PdCl_2(PhCN)_2$ at 0 °C in 80–85% isolated yield [45]. The dimeric thiopalladacycle was then used for a Heck-type coupling with an alkene to give a 2,3-disubstituted benzo[*b*]thiophene (Scheme 1).

Various reaction conditions were examined to optimize the Heck-type coupling, including the effect of solvents, ancillary ligands, temperature and reaction time. The highest yield of the desired 3-alkenylbenzo[*b*]thiophene product was obtained from the reaction of the thiopalladacycle and *n*-butyl acrylate (10 equiv) in THF at 70 °C for 3 h in the presence of benzoquinone (2 equiv). However, the Heck-coupled product obtained from this reaction was unstable and could not be isolated. It was assumed the highly unstable nature of the product was due to the presence of imine moiety in the alkenylated benzothiophene adduct. To overcome this problem, the imine in the alkenylated benzo[*b*]thiophene adduct was reduced in situ to the corresponding secondary amine. Of the various reducing agents used, a combination of $NaBH_3CN$ (4 equiv) in glacial acetic acid and methanol (1:3) at 0 °C was found to give greatest yield of the 3-alkenylbenzo[*b*]thiophene (35%). The preparation of pure thiopalladacycle for proceeding the coupling reaction and low yield of the coupling product shows unattractive protocol for the synthesis of 3-alkenylbenzo[*b*]thiophene.

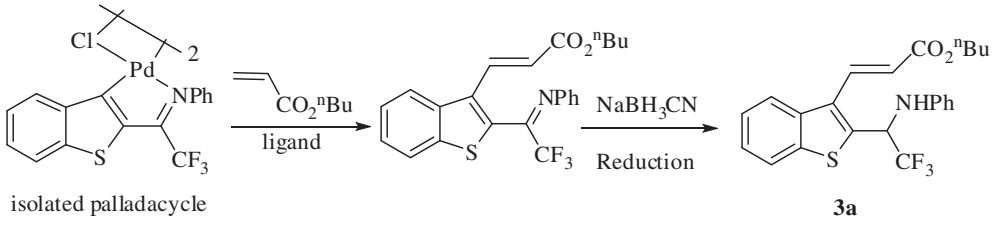
To surmount the demerits of the reaction as observed above, an alternate protocol was investigated for the efficient synthesis of 3-alkenylbenzo[*b*]thiophene. Reaction of thioanisole-substituted propargyl imine with *n*-butyl acrylate in the presence of $PdCl_2(PhCN)_2$ and benzoquinone at 70 °C and subsequent reduction of the imine with $NaBH_3CN$/acetic acid, gave the desired coupled product in good to high yields (Scheme 2).

In order to optimize the reaction conditions, various palladium salts, ancillary ligands, solvents and temperatures were investigated to obtain the best yield of the desired product (Table 1).

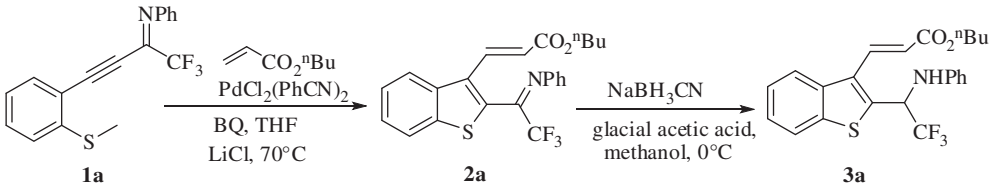
It was found that the best reaction condition for the coupling of thioanisole perfluoroalkyl propargyl imine **1a**, used *bis*-(benzonitrile) palladium dichloride (1 equiv), *n*-butyl acrylate (10 equiv), benzoquinone (2 equiv) and LiCl (2 equiv) in THF at 70 °C. The subsequent reduction with $NaBH_3CN$ (4 equiv) in a mixture of glacial acetic acid and methanol (1:3) at 0 °C afforded the 3-alkenylbenzo[*b*]thiophene in 63% yield. In two separate experiments, the reaction was also carried out using 10 mol% catalytic amount of $PdCl_2(PhCN)_2$ with 5 equiv and 10 equiv of *n*-butyl acrylate (Table 1, entries 3 and 4) under the same reaction conditions, but only low yields of the desired product were obtained. 2,3-disubstituted benzothiophene, **3a** was characterized by ^1H and ^{13}C NMR, mass spectrometry and the structure confirmed by X-ray diffraction analysis (Fig. 2).

To explore the scope of the coupling reaction, several alkenes were tested with thioanisole-substituted propargyl imines under optimized conditions and the results are presented in Table 2. It is clear from the Table 2, that α,β-unsaturated esters like *n*-butyl acrylate (Table 2, entry 1) and methyl acrylate (Table 2, entry 2), afforded good yields of the coupled product while acrylonitrile and styrene only gave, 51% and 56% yields, respectively (Table 2, entries 3, 4). The effect of various substituents on aryl imine was also studied. Aryl imines containing electron-withdrawing groups and weakly electron-donating group (methyl group) gave the coupled product in moderate yields (Table 2, entries 5, 6 and 7), while there was no coupling product observed with aryl imine containing methoxy group (electron-donating group) (Table 2, entry 10). Good yields were obtained from coupling thioanisole-substituted propargyl imines with alkene containing long chain perfluoroalkyl groups (C_2F_5–C_4F_9) and with methyl acrylate (Table 2, entries 8–9). However, in the case of acrylamide (Table 2, entry 11), methyl vinyl ketone (Table 2, entry 12) and *N*, *N*-dimethyl acrylamide (entry 13), no corresponding coupled product was obtained using the same optimized reaction conditions.

Taking advantage of our combined strategy for the synthesis of substituted benzo[*b*]thiophenes, we focused our attention towards the synthesis of 3-alkenylbenzo[*b*]selenophenes (Scheme 3). Selenoanisole-substituted propargyl imines were prepared in a similar fashion as compound **1a**. The optimized reaction conditions determined for the Heck-type coupling were applied to various selenoanisole perfluoroalkyl propargyl imines and alkenes



Scheme 1. Heck-type coupling of dimeric thiopalladacycle with *n*-butyl acrylate.



Scheme 2. Heck-type coupling of thioanisole substituted perfluoroalkyl propargyl imines (**1a**) with *n*-butyl acrylate.

(see the Experimental section for a typical procedure). Aryl imines containing electron-withdrawing groups afforded good yields of the benzo[*b*]selenophenes while those containing electron-donating groups failed to give any coupled product (Fig. 3).

Table 2 and Fig. 3 show the high stereoselectivity of the Heck-type coupling reaction of substituted propargyl imines with alkenes. In all cases, exclusive formation of the (*E*)-isomer of 3-alkenylbenzo[*b*]thiophenes and 3-alkenylbenzo[*b*]selenophenes was observed [29].

The above mentioned results for the synthesis of 3-alkenylbenzo[*b*]thiophene indicate the formation and involvement of the thiopalladacycle as the key step of the Heck-type coupling. Thus the first step involves the coordination of the N atom in the imine to palladium followed by the interaction of the triple bond to the electrophilic Pd center. The thiopalladacycle generated in the reaction undergoes alkene insertion, followed by Pd–H elimination with the release of the 3-alkenylbenzo[*b*] thiophene.

Though the role of benzoquinone as an oxidant is well established in the literature [50,51], in the present Heck-type coupling reaction it acts as a stabilizing ligand [52]. To confirm the role of benzoquinone, we conducted a series of reactions in which cyclic unsaturated enones such as maleic anhydride and cyclohexenone were used in place of benzoquinone. The results obtained from these reactions suggest that benzoquinone, maleic anhydride and cyclohexenone act as stabilizing ligand to palladium during the coupling reaction. Furthermore, in the absence of these ligands, the Heck-type coupling reaction does not proceed at all.

3. Conclusion

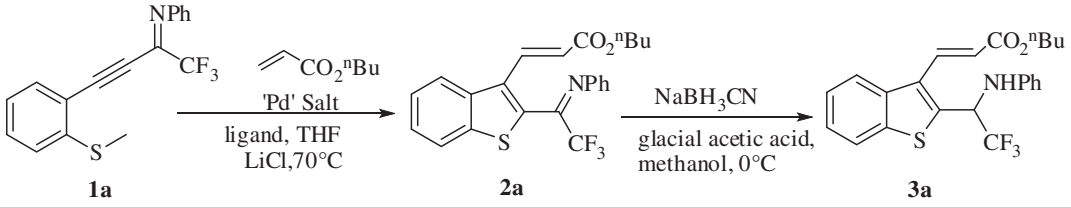
In conclusion, a new methodology for the synthesis of perfluoroalkyl 3-alkenylbenzo[*b*]thiophenes and 3-alkenylbenzo[*b*] selenophenes has been developed using one pot Heck-type coupling reaction of an alkene and the corresponding heteroatom substituted propargyl imine. This methodology enables the synthesis of structurally diverse 3-alkenylbenzo[*b*]thiophenes and 3-alkenylbenzo[*b*]selenophenes to give the (*E*)-isomers exclusively using various alkynes, perfluoroalkyl groups, substituted anilines and alkenes. Investigations towards the catalytic use of palladium salts and the bio-activity of these 3-alkenylbenzo[*b*]thiophenes and 3-alkenylbenzo[*b*]selenophenes are in progress.

4. Experimental section

4.1. General

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen. Chemicals were purchased from Aldrich and used as it is unless mentioned otherwise. All solvents used for reactions were dried before use. Product purification by column chromatography was accomplished using silica gel 60–120 mesh. Technical grade solvents were used for chromatography and distilled prior to use. NMR spectra were recorded in Fourier transform mode. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker-Avance (300 MHz), Varian-Inova (400 MHz) and Varian-Inova (500 MHz) spectrometers in $CDCl_3$ and $CFCl_3$ solvents and

Table 1
Optimization study for the Heck-type coupling of thioanisole-substituted perfluoroalkyl propargyl imine, **1a** with *n*-butyla crylate.[a]



Entry	Palladium salt	Ligand	Solvent	Temp.(°C)	Time(h)	(**3a**)Yield%[b]
1	$PdCl_2$	BQ	DMF	90	12	18[c]
2	Pd $(OAc)_2$	BQ	THF	70	12	20[c]
3	$PdCl_2$ $(PhCN)_2$	BQ	THF	70	12	25[c]
4	$PdCl_2$ $(PhCN)_2$	BQ	THF	70	12	28[d]
5	$PdCl_2$	BQ	THF	70	6	31
6	$PdCl_2$ $(PhCN)_2$	BQ	THF:CH_3CN (9:1)	70	5	41
7	$PdCl_2$ $(PhCN)_2$	BQ	THF	70	5	63
8	$PdCl_2$ $(PhCN)_2$	MA	THF	70	5	61
9	$PdCl_2$ $(PhCN)_2$	MA	THF	70	5	59[e]
10	$PdCl_2$ $(PhCN)_2$	cyclohexenone	THF	70	5	55

BQ = benzoquinone; MA = maleic anhydride.
[a] Reaction conditions: **1a** (0.25 mmol), *n*-butyl acrylate (10 equiv), Pd(II) salt (1 equiv), ligand (2 equiv), LiCl (2 equiv), solvent (2 mL).
[b] Isolated yields.
[c] Pd(II) salt (10 mol%), *n*-butyl acrylate (5 equiv).
[d] Pd(II) salt (10 mol%), *n*-butyl acrylate (10 equiv).
[e] Under N_2 atmosphere.

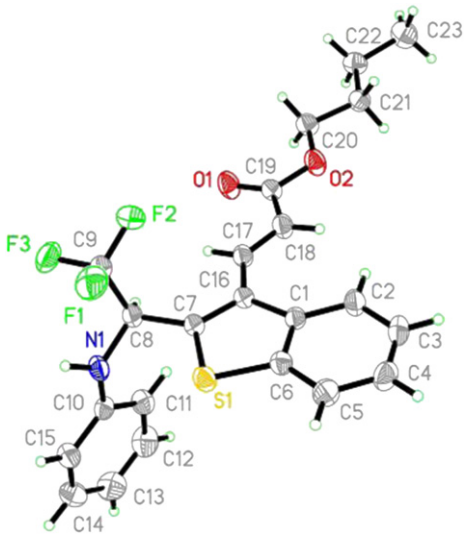


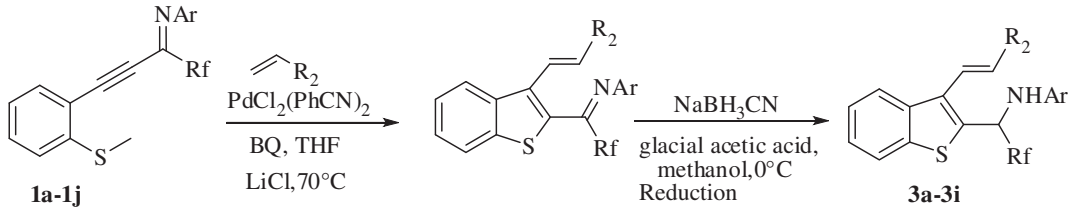
Fig. 2. Ortep diagram of compound **3a**.

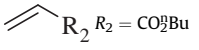
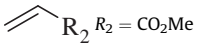
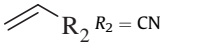
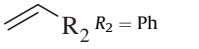
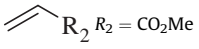
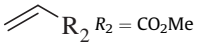
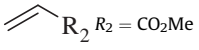
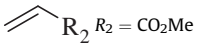
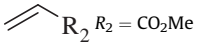
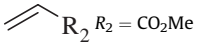
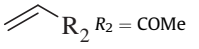
TMS as the internal standard. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, br = broad; coupling constants are reported in Hz. Infrared spectra were recorded on a Thermo Nicolet Nicolet Nexus 670 spectrometer and reported in cm^{-1}. Low (MS) and high resolution mass spectra (HRMS) were recorded on a Waters 2695 and Thermo Scientific Exactive spectrometer respectively and mass/charge (m/z) ratios are reported as values in atomic mass units. Melting points were recorded on a Toshniwal melting point apparatus. *N*-aryl perfluoroalkyl propargyl imines were prepared by the Sonogashira coupling of imidoyl iodide and alkyne according to the literature procedure [53].

4.2. Typical procedure for the N-aryl perfluoroalkyl propargyl imines

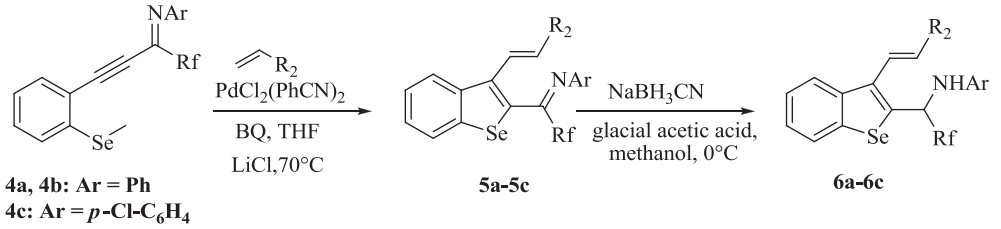
To a stirred mixture of $PdCl_2$ $(PPh_3)_2$ (2 mol%), CuI (4 mol%) in Et_3N (4 mL), alkyne (1 mmol) and *N*-aryl perfluoroalkyl imidoyl iodide (1 mmol) were added successively under N_2 atmosphere. The mixture was stirred at room temperature until the starting materials

Table 2
Heck-type coupling of thioanisole-substituted propargyl imines with alkenes[a].



Entry	Ar	Rf	Alkene	Product	Yield (%)[b]
1	Ph (**1a**)	CF_3	 R_2 = CO_2^nBu	**3a**	63
2	Ph (**1a**)	CF_3	 R_2 = CO_2Me	**3b**	73
3	Ph (**1a**)	CF_3	 R_2 = CN	**3c**	51
4	Ph (**1a**)	CF_3	 R_2 = Ph	**3d**	56
5	4-F-Ph (**1e**)	CF_3	 R_2 = CO_2Me	**3e**	50
6	4-Cl-Ph (**1f**)	CF_3	 R_2 = CO_2Me	**3f**	44
7	4-Me-Ph (**1g**)	CF_3	 R_2 = CO_2Me	**3g**	40
8	Ph (**1h**)	C_2F_5	 R_2 = CO_2Me	**3h**	79
9	Ph (**1i**)	C_4F_9	 R_2 = CO_2Me	**3i**	76
10	4-OMe-Ph (**1j**)	CF_3	 R_2 = CO_2Me	NR	–
11	Ph (**1a**)	CF_3	 $CONH_2$	NR	–
12	Ph (**1a**)	CF_3	 R_2 = COMe	NR	–
13	Ph (**1a**)	CF_3	 $CONMe_2$	NR	–

For reduction of imine: $NaBH_3CN$ (4 equiv), methanol (1.5 mL), glacial acetic acid (0.5 mL) at 0 °C for 1 h.
[a] Reaction conditions: Propargyl imine (0.25 mmol), alkene (10 equiv), $PdCl_2(PhCN)_2$ (1 equiv), benzoquinone (2 equiv), LiCl (2 equiv), THF (2 mL) at 70 °C for 5 h.
[b] Isolated yields. NR = no reaction.



Scheme 3. Heck-type coupling of selenoanisole substituted propargyl imines with alkenes.

are consumed. The reaction mixture was filtered and solvent was removed from filtrate. The crude product obtained was purified by column chromatography using hexane-ethyl acetate mixture.

4.3. Characterization of the compounds 1a, 1e–1h, 4a and 4c

4.3.1. (Phenyl)-[3-(2-methylthio-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-amine (1a)

Yield: 79%; Yellow solid. Mp: 89–91 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (*t*, *J* = 7.8 Hz, 2H), 7.37–7.31 (m, 4H), 7.27–7.23 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.06 (*t*, *J* = 7.8 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 147.4, 144.2, 135.8 (*q*, *J* = 37 Hz), 134.0, 131.1, 128.8, 127.3, 124.6, 124.3, 121.5, 118.0, 115.0 (*q*, *J* = 278.8), 97.4, 84.1, 15.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −70.99 (s, 3F). FTIR (KBr): 2923, 2185, 1608, 1220, 1135 cm^{-1}. MS (ESI): *m*/*z* = 320 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{17}H_{13}F_3NS$ $[M + H]^+$ 320.0715; Found 320.0713.

4.3.2. (4-Fluoro-phenyl)-[3-(2-methylthio-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-amine (**1e**)

Yield: 82%; Yellow solid. Mp: 86–88 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.43 (m, 2H), 7.40–7.32 (m, 2H), 7.17–7.05 (m, 4H), 2.45 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 161.9 (d, *J* = 248.8 Hz), 144.2, 143.3, 138.6 (*q*, *J* = 39 Hz), 134.1, 131.3, 124.5 (d, *J* = 18.1 Hz), 124.1, 124.0, 118.7 (*q*, *J* = 277.9 Hz), 117.9, 115.7 (d, *J* = 22.7 Hz), 97.9, 84.8, 15.1. ^{19}F NMR (376.3 MHz, $CDCl_3$): −70.91 (s, 3F), −113.76–113.85 (m, 1F). FTIR (KBr): 2924, 2189, 1614, 1575, 1269 cm^{-1}. MS (ESI): *m*/*z* = 338 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{17}H_{12}F_4NS$ $[M + H]^+$ 338.0621; Found 338.0620.

4.3.3. (4-Chloro-phenyl)-[3-(2-methylthio-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-amine (**1f**)

Yield: 80%; Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.46 (m, 1H), 7.39–7.27 (m, 3H), 7.23–7.16 (m, 2H), 7.16–7.04 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.4, 134.1, 133.5 (*q*, *J* = 39.5 Hz), 131.4, 130.1, 129.5, 127.2, 127.1, 124.5, 124.4, 124.3, 120.3 (*q*, *J* = 289.8 Hz), 98.7, 84.4, 15.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): −71.02 (s, 3H). FTIR (KBr): 2923, 2187, 1619, 1273 cm^{-1}. MS (ESI): *m*/*z* = 354 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{17}H_{12}F_3NClS$ $[M + H]^+$ 354.0325; Found 354.0326.

4.3.4. (4-Methyl-phenyl)-[3-(2-methylthio-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-amine (**1g**)

Yield: 73%; Yellow solid. Mp: 58–60 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.34 (m, 4H), 7.25–7.16 (m, 3H), 7.10 (*t*, *J* = 7.5 Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.6, 144.0, 138.0, 137.1 (*q*, *J* = 39.6 Hz), 133.9, 131.0, 129.4, 124.6, 124.4, 122.2, 118.3, 115.2 (*q*, *J* = 277.2 Hz), 97.3, 85.2, 21.2, 15.1. ^{19}F NMR (376.3 MHz, $CDCl_3$): −70.79 (s, 3H). FTIR (KBr): 2963, 2923, 2184, 1606, 1575, 1266 cm^{-1}. MS (ESI): *m*/*z* = 334 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{18}H_{15}F_3NS$ $[M + H]^+$ 334.0871; Found 334.0870.

4.3.5. [3-(2-methylsulfanyl-phenyl)-1-pentafluoroethyl-prop-2-ynylidene]-phenyl-amine (**1h**)

Yield: 78%; Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.28 (m, 7H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.08 (*t*, *J* = 7.5 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 147.6144.1, 139.5 (*t*, *J* = 28.6 Hz), 134.0, 131.2, 128.8, 127.5, 124.5, 124.3, 121.5, 120.5, 118.0, 116.74, 98.1, 85.1, 15.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): −81.54 (*t*, *J* = 1.9 Hz, 2F), −116.20–116.24 (m, 3F). FTIR (KBr): 2925, 2191, 1609, 1206 cm^{-1}. MS (ESI): *m*/*z* = 370 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{18}H_{13}F_5NS$ $[M + H]^+$ 370.0683; Found 370.0687.

4.3.6. [3-(2-methylseleno-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-phenyl-amine (**4a**)

Yield: 76%; Yellow solid. Mp: 80–82 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (*t*, *J* = 7.6 Hz, 2H), 7.35–7.23 (m, 6H), 2.28 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 147.5, 138.1 (*q*, *J* = 28.5 Hz), 134.2, 131.1, 128.9, 128.5, 127.4, 125.4, 121.3, 120.5, 119.5, 115.0 (*q*, *J* = 282 Hz), 98.1, 83.9, 6.4. ^{19}F NMR (376.3 MHz, $CDCl_3$): −71.38 (s, 3H). FTIR (KBr): 2923, 2853, 2183, 1608, 1265 cm^{-1}. MS (ESI): *m*/*z* = 368 $[M + H]^+$. HRMS: *m*/*z* calcd for $C_{17}H_{13}F_3NSe$ $[M + H]^+$ 368.0160; Found 368.0161.

4.3.7. (4-Chloro-phenyl)-[3- (2-methylseleno-phenyl)-1-trifluoromethyl-prop-2-ynylidene]-amine (**4c**)

Yield: 74%; Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.45 (m, 1H), 7.35–7.27 (m, 4H), 7.24–7.09 (m, 3H), 2.27 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 145.5, 142.4 (*q*, *J* = 39 Hz), 138.6, 134.3, 131.4, 130.1, 128.3, 127.3, 127.2, 125.7, 125.4, 120.3 (*q*, *J* = 278 Hz), 99.4, 83.5, 6.5. ^{19}F NMR (376.3 MHz, $CDCl_3$): −70.99 (s, 3F). FTIR (KBr):

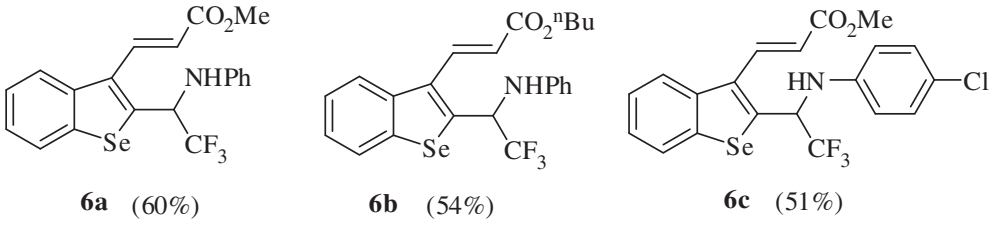


Fig. 3. Synthesis of 3-alkenylbenzo[*b*]selenophenes.

2927, 2853, 1620, 1271 cm^{-1}. MS (ESI): $m/z = 401$ $[M + H]^+$. HRMS: m/z calcd for $C_{17}H_{12}F_3NClSe$ $[M + H]^+$ 401.9770; Found 401.9767.

4.4. Typical procedure for the Heck-type coupling of N-aryl perfluoroalkyl propargyl imines and alkenes

To a solution of *N*-aryl perfluoroalkyl propargyl imine (0.25 mmol) in dry THF (2 mL) was added $PdCl_2(PhCN)_2$ (0.25 mmol), benzoquinone (2 equiv), LiCl (2 equiv) and alkene (10 equiv) successively and the mixture was stirred at 70 °C for 5 h. The mixture was allowed to cool to room temperature and partially concentrated under reduced pressure.

The imine solution was diluted with methanol (1.5 mL) and $NaBH_3CN$ (4 equiv) was added at 0 °C over 15 min followed by glacial acetic acid (0.5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h, then filter through celite bed with EtOAc (25 mL). The organic filtrate was washed with saturated aqueous $NaHCO_3$ followed by brine solution. The separated organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the product was purified by column chromatography, eluting with EtOAc/hexane (1:99).

4.5. Characterization of the compounds 3a–3i and 6a–6c

4.5.1. (E)-butyl 3-(2-(2,2,2-trifluoro-1-(phenylamino)ethyl)benzo [b]thiophen-3-yl)acrylate (**3a**)

Yield: 63%; Yellow solid. Mp: 80–82 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.79 (d, $J = 7.4$ Hz, 1H), 7.46–7.36 (dqt, $J = 7.2$ Hz, 1.3 Hz, 2H), 7.14 (*t*, $J = 7.6$ Hz, 2H), 6.78 (*t*, $J = 7.4$ Hz, 1H), 6.60 (d, $J = 7.9$ Hz, 2H), 6.45 (d, $J = 16.2$ Hz, 1H), 5.52 (qt, $J = 6.8$ Hz, 1H), 4.33–4.21 (m, 3H), 1.74 (qt, $J = 6.8$ Hz, 2H), 1.55–1.41 (m, 2H), 1.02 (*t*, $J = 7.4$ Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.6, 144.5, 139.5, 138.9, 137.6, 135.1, 131.4, 129.5, 125.7, 125.2, 124.4 (*q*, $J = 283.2$ Hz), 123.2, 123.0, 122.7, 120.1, 114.1, 64.9, 55.7 (*q*, $J = 30.7$ Hz), 30.7, 19.2, 13.7.^{19}F NMR (376.3 MHz, $CDCl_3$) δ −73.77 (d, $J = 6.2$ Hz, 3F). FTIR (KBr): 3365 (s), 1704 (s) cm^{-1}. MS (ESI): $m/z = 456$ $[M + Na]^+$. HRMS: m/z Calcd for $C_{23}H_{22}O_2SF_3$ $[M + Na]^+$ 456.1221; Found 456.1233.

4.5.2. (E)-methyl 3-(2-(2,2,2-trifluoro-1-(phenylamino)ethyl)benzo [b]thiophen-3-yl) acrylate (**3b**)

Yield: 73%; Yellow solid. Mp: 82–84 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.92 (m, 2H), 7.78 (d, $J = 7.7$ Hz,1H), 7.44–7.35 (m, 2H), 7.13 (*t*, $J = 7.7$ Hz, 2H), 6.77 (*t*, $J = 7.7$ Hz, 1H), 6.59 (d, $J = 7.7$ Hz, 2H), 6.46 (d, $J = 16.4$ Hz, 1H), 5.50 (qt, $J = 6.7$ Hz, 1H), 4.28 (d, $J = 6.7$ Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 144.4, 139.8, 138.9, 137.6, 135.4, 131.3, 129.5, 125.7, 125.2, 124.3 (*q*, $J = 283.2$ Hz), 122.9, 122.7, 122.5, 120.2, 114.1, 55.7 (*q*, $J = 31.8$ Hz), 52.0. ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.77 (d, $J = 6.2$ Hz, 3F). FTIR (KBr): 3385 (s), 1703 (s) cm^{-1}. MS (ESI): $m/z = 414$ $[M + Na]^+$. HRMS: m/z Calcd for $C_{20}H_{16}F_3NO_2S$ $[M + Na]^+$ 414.0751; Found 414.0749.

4.5.3. (E)-3-(2-(2,2,2-trifluoro-1-(phenylamino)ethyl)benzo[b] thiophen-3-yl)acrylo-nitrile (**3c**)

Yield: 51%; Yellow solid. Mp: 104–106 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.78 (m, 2H), 7.67 (d, $J = 16.6$ Hz, 1H), 7.48–7.38 (m, 2H), 7.16 (*t*, $J = 7.7$ Hz, 2H), 6.82 (*t*, $J = 7.4$ Hz, 1H), 6.59 (d, $J = 7.7$ Hz, 2H), 5.92 (d, $J = 16.6$ Hz, 1H), 5.38 (qt, $J = 6.6$ Hz, 1H), 4.27 (d, $J = 6.6$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.2, 141.5, 140.8, 139.7, 138.9, 136.9, 129.6, 126.1, 125.7, 124.1 (*q*, $J = 283.2$ Hz), 122.9, 122.4, 120.5, 117.5, 114.1, 101.6, 55.9 (*q*, $J = 31.8$ Hz). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −73.69 (d, $J = 7.4$ Hz, 3F). FTIR (KBr): 3335 (s), 2214 (s) cm^{-1}. MS (ESI): $m/z = 381$ $[M + Na]^+$. HRMS: m/z Calcd for $C_{19}H_{13}F_3N_2S$ $[M + Na]^+$ 381.0649; Found 381.0648.

4.5.4. (E)-N-(2,2,2-trifluoro-1-(3-styrylbenzo[b]thiophen-2-yl) ethyl)benzenamine (**3d**)

Yield: 56%; Yellow solid. Mp: 146–148 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, $J = 7.7$ Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.55 (d, $J = 6.9$ Hz, 2H), 7.48–7.33 (m, 2H), 7.29–7.02 (m, 8H), 6.92 (*t*, $J = 7.2$ Hz, 1H), 6.82 (s, 1H), 5.54 (*q*, $J = 6.9$ Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5, 140.7, 140.5, 137.1, 135.2, 131.5, 129.1, 128.6, 128.3, 127.5, 126.8, 125.2, 124.9 (*q*, $J = 286.5$ Hz), 124.7, 123.9, 123.2, 122.9, 121.6, 118.6, 105.7, 63.8 (*q*, $J = 32.9$ Hz). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −77.08 (d, $J = 7.4$ Hz, 3F). FTIR (KBr): 1727 (s) cm^{-1}. MS (ESI): $m/z = 410$ $[M + H]^+$. Anal. Calcd. for $C_{24}H_{18}F_3NS$: C 70.04, H 4.34, N 3.12; Found C 70.01, H 4.33, N 3.17.

4.5.5. (E)-methyl 3-(2-(2,2,2-trifluoro-1-(4-fluorophenylamino) ethyl)-benzo[b] thiophen-3-yl)acrylate (**3e**)

Yield: 50%; Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95–7.88 (m, 2H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.44–7.36 (m, 2H), 6.84 (*t*, $J = 8.6$ Hz, 2H), 6.58–6.53 (m, 2H), 6.43 (d, $J = 16.4$ Hz, 1H), 5.41 (qt, $J = 6.7$ Hz, 1H), 4.15 (d, $J = 6.7$ Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 157.2 (d, $J = 139.3$ Hz), 140.7, 139.3, 138.9, 137.5, 135.3, 131.5, 125.8, 125.3, 122.9, 122.8, 122.7, 122.4 (*q*, $J = 283.2$), 116.1 (d, $J = 21.9$ Hz), 115.6 (d, $J = 6.6$ Hz), 56.5 (*q*, $J = 30.7$ Hz), 52.0. ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.76 (d, $J = 6.1$ Hz, 3F), −124.53–124.62 (m, 1F). FTIR (KBr): 3379, 1711 (s) cm^{-1}. MS (ESI): $m/z = 432$ $[M + Na]^+$. HRMS: m/z Calcd for $C_{20}H_{15}F_4NO_2S$ $[M + Na]^+$ 432.0657; Found 432.0658.

4.5.6. (E)-methyl 3-(2-(1-(4-chlorophenylamino)-2,2,2-trifluoroethyl)-benzo [b]thiophen-3-yl)acrylate (**3f**)

Yield: 44%; Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97–7.89 (m, 2H), 7.81–7.76 (m, 1H), 7.46–7.35 (m, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.53 (d, $J = 8.8$ Hz, 2H), 6.44 (d, $J = 16.2$ Hz, 1H), 5.44 (qt, $J = 6.8$ Hz, 1H), 4.29 (d, $J = 7.4$ Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.8, 143.1, 138.9, 137.5, 135.3, 131.6, 129.4, 125.8, 125.4, 125.1, 124.3 (*q*, $J = 282.6$ Hz), 123.1, 122.7, 122.5, 122.4, 115.3, 55.9 (*q*, $J = 31.8$ Hz), 52.0. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −73.72 (d, $J = 7.4$ Hz, 3F). FTIR (KBr): 3362 (s), 1712 (s) cm^{-1}. MS (ESI): $m/z = 448$ $[M + Na]^+$. HRMS: m/z Calcd for $C_{20}H_{15}ClF_3NO_2S$ $[M + Na]^+$448.0361; Found 448.0351.

4.5.7. (E)-methyl 3-(2-(2,2,2-trifluoro-1-p-tolylethylamino)benzo [b]thiophen-3-yl)acrylate (**3g**)

Yield: 40%; Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04–7.91 (m, 2H), 7.79 (d, $J = 7.4$ Hz, 1H), 7.48–7.35 (m, 2H), 6.96 (d, $J = 8.1$ Hz, 2H), 6.58–6.46 (m, 3H), 5.49 (qt, $J = 6.8$ Hz, 1H), 4.26 (d, $J = 6.9$ Hz, 1H), 3.87 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 142.1, 140.0, 138.9, 137.6, 135.4, 131.2, 129.9, 129.6, 126.2, 125.6, 125.1, 123.9 (*q*, $J = 288.0$ Hz), 122.9, 122.7, 114.4, 56.2 (*q*, $J = 31.9$ Hz), 51.9, 20.3. ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.8 (d, $J = 7.3$ Hz, 3F). FTIR (KBr): 3406, 1714 (s) cm^{-1}. MS (ESI): $m/z = 406$ $[M + H]^+$. Anal. Calcd. for $C_{21}H_{18}F_3NO_2S$: C 62.22, H 4.44, N 3.45; Found C 62.20, H 4.43, N 3.43.

4.5.8. (E)-methyl 3-(2-(2,2,3,3,3-pentafluoro-1-(phenylamino) propyl)benzo[b]-thiophen-3-yl)acrylate (**3h**)

Yield: 79%; Yellow solid. mp: 90–92 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94–7.88 (m, 2H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.43–7.34 (m, 2H), 7.12 (*t*, $J = 7.8$ Hz, 2H), 6.76 (*t*, $J = 6.8$ Hz, 1H), 6.58 (d, $J = 8.8$ Hz, 2H), 6.42 (d, $J = 15.7$ Hz, 1H), 5.67–5.58 (m, 1H), 4.16 (d, $J = 8.8$ Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.8, 143.9, 139.0, 137.5, 135.3, 129.5, 126.4 (*q*, $J = 287.6$ Hz), 125.7, 125.2, 122.9, 122.6, 122.4, 122.1, 120.3, 119.9, 116.6, 114.2, 53.4 (m), 52.0. ^{19}F NMR

(376.3 MHz, $CDCl_3$) δ −81.62 (s, 3F), −115.79 (dd, J = 6.2, 275.6 Hz, 1F), −126.59 (dd, J = 19.7, 275.6 Hz, 1F). FTIR (KBr): 3387 (s), 1707 (s) cm^{-1}. MS (ESI): m/z = 464 $[M + Na]^+$. HRMS: m/z Calcd for $C_{21}H_{16}F_5NO_2S$ $[M + Na]^+$ 464.0719; Found 464.0717.

*4.5.9. (E)-methyl 3-(2-(2,2,3,3,4,4,5,5,5-nonafluoro-1-(phenylamino)pentyl)benzo[b] thiophen-3-yl)acrylate (**3i**)*

Yield: 76%; Yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.88 (m, 2H), 7.75 (dd, J = 6.8, 2.3 Hz, 1H), 7.42–7.32 (m, 2H), 7.12 (t, J = 7.6 Hz, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.58 (d, J = 7.6 Hz, 2H), 6.42 (d, J = 15.9 Hz, 1H), 5.81–5.68 (m, 1H), 4.20 (d, J = 9.8 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.4, 143.9, 139.1, 138.9, 137.6, 135.4, 131.9, 129.7, 125.8, 125.7, 125.3, 123.7, 123.2, 123.1, 122.7, 120.5, 114.3, 53.4 (m), 51.9. ^{19}F NMR (400 MHz, $CDCl_3$): δ −81.17 (t, J = 12.3 Hz, 3F), −111.70––112.96 (m,1F), −121.50––122.29 (m, 1F), −122.62––122.96 (m, 2F), −124.98––127.72 (m, 2F). FTIR (KBr): 3366 (s), 1716 (s) cm^{-1}. MS (ESI): miz = 564 $[M + Na]^+$. HRMS: m/z Calcd for $C_{23}H_{16}F_9NO_2S$ $[M + Na]^+$ 564.0655; Found 564.0640.

*4.5.10. (E)-methyl 3-(2-(2,2,2-trifluoro-1-(phenylamino)ethyl) benzo[b]selenophen-3-yl)acrylate (**6a**)*

Yield: 60%; Pale brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89–7.75 (m, 3H), 7.40–7.24 (m, 3H), 7.10 (t, J = 7.6 Hz, 2H), 6.75 (t, J = 7.4 Hz, 1H), 6.56 (d, J = 7.7 Hz, 2H), 6.32 (d, J = 16.1 Hz, 1H), 5.39 (q, J = 6.6 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.8, 144.6, 140.5, 140.2, 137.0, 134.7, 129.5, 126.2, 125.9, 125.7, 125.2, 124.8, 123.8, 123.6 (q, J = 285.4 Hz), 120.2, 114.2, 57.3 (q, J = 30.7 Hz), 52.0. ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.78 (d, J = 6.2, 3F). FTIR (KBr): 3376, 1714 (s) cm^{-1}. MS (ESI): m/z 440 $[M + H]^+$. HRMS: m/z Calcd for $C_{20}H_{17}F_3NO_2Se$ $[M + H]^+$ 440.0376; Found 440.0387.

*4.5.11. (E)-butyl 3-(2-(2,2,2-trifluoro-1-(phenylamino)ethyl)benzo [b]selenophen-3-yl)acrylate (**6b**)*

Yield: 54%; Brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.73 (m, 3H), 7.40–7.24 (m, 2H), 7.09 (t, J = 7.6 Hz, 2H), 6.74 (t, J = 7.4 Hz, 1H), 6.56 (d, J = 7.7 Hz, 2H), 6.30 (d, J = 16.2 Hz, 1H), 5.39 (q, J = 6.2 Hz, 1H), 4.28–4.14 (m, 2H), 1.65 (qt, J = 6.8 Hz, 2H), 1.45–1.33 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.4, 144.6, 143.5, 140.5, 136.7, 134.8, 129.5, 125.9, 125.6, 125.2, 124.9, 124.3, 123. 5 (q, J = 292.0 Hz), 120.2, 119.9, 114.1, 64.9, 57.2 (q, J = 30.7 Hz), 30.6, 19.2, 13.7. ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.81 (d, J = 6.2 Hz, 3F). FTIR (KBr): 3365, 1711 (s) cm^{-1}. MS (ESI): m/z 482 $[M + H]^+$. HRMS: m/z Calcd for $C_{23}H_{23}F_3NO_2Se$ $[M + H]^+$ 482.0846; Found 482.0869.

*4.5.12. (E)-methyl 3-(2-(1-(4-chlorophenylamino)-2,2,2-trifluoroethyl)benzo[b]-selenophen-3-yl)acrylate (**6c**)*

Yield: 51%; Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92–7.80 (m, 3H), 7.45–7.30 (m, 2H), 7.11 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 8.7 Hz, 2H), 6.33 (d, J = 16.1 Hz, 1H), 4.26 (d, J = 4.7 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.6, 143.2, 142.7, 140.1, 136.9, 135.1, 129.4, 126.1, 125.8, 125.7, 125.3, 125.2, 124.9, 124.2, 123.8 (q, J = 271.8 Hz), 115.5, 57.4 (q, J = 31.4 Hz), 52.0. ^{19}F NMR (400 MHz, CDCl3): δ −73.80 (d, J = 7.4 Hz, 3F). FTIR (KBr): 3363, 1719 (s) cm^{-1}. MS (ESI): m/z 474$[M + H]^+$. HRMS: m/z Calcd for $C_{20}H_{16}F_3NO_2ClSe$ $[M + H]^+$ 473.9986; Found 473.9979.

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