Double C–H bond functionalization for C–C coupling at the β-position of thiophenes using palladium-catalyzed 1,4-migration associated with direct arylation†

Linhao Liu, Marie Cordier, Thierry Roisnel and Henri Doucet*

The functionalization of C–H bonds at β-positions of 5-membered ring heteroarenes such as thiophene is generally more challenging than at α-positions. By using Pd-catalyzed 1,4-migration associated with direct arylation, under appropriate conditions, the functionalization of such thienyl β-positions of 2-arythiophenes is possible. The oxidative addition of 2-(2-bromoaryl)thiophenes to palladium followed by Pd 1,4-migration activates these β-positions. Then, Pd-catalyzed direct coupling with heteroarenes provides β-heteroarylated 2-arythiophene derivatives. In the course of this coupling reaction, a new C–C bond arises from the functionalization of two C–H bonds. Conversely, the Suzuki reaction using such 2-(2-bromoaryl)thiophenes provides 1,2-diheteroaryl-substituted benzene derivatives. These regiodivergent heteroarylations tolerate a range of substituents on the benzene ring and also several heteroarenes and provide a new route to π-extended polycyclic heteroaromatics. Moreover, these procedures employ easily available air-stable catalysts and inexpensive bases.

Introduction

When specific C–H bonds of organic molecules can be directly functionalized via catalytic reactions, it often provides simple synthetic methods.1 Metal-catalyzed C–H bond activation/functionalization of heteroarenes, reported by Ohta et al. 1990, now represents one of the most effective methods for the preparation of heteroarylated arenes.2 For such coupling reactions, initially in most cases, only the “most reactive” C–H bond of (hetero)arenes could be functionalized.3–7 Nevertheless, the C–H bond functionalization methodology will only be really synthetically useful when it will be possible to activate a specific C–H bond on the molecules. Therefore, the discovery of conditions allowing the regioselective functionalization of several bonds of the same molecule, also called regiodivergent functionalization, is a very important aspect of the current research on metal-catalyzed reactions.

So far, the Pd-catalyzed reactions such as Suzuki coupling of heteroaryllboronic acids with thiophenes bearing a 2-halo-benzene substituent selectively lead to 1,2-diheteroarylated benzene derivatives (Scheme 1a).8 On the other hand, the C3-heteroarylation of 2-aryl-3-halothiophenes for the access to the corresponding heteroaryl-substituted thiophene derivatives via metal-catalyzed reactions has been rarely described (Scheme 1b).9,10 This might be due to the tedious multi-step route to many 3-halothiophene derivatives.11 To the best of our knowledge, the synthesis of 2-aryl-3-heteroaryltiophenes from 2-(2-bromoaryl)thiophenes has not been reported so far (Scheme 1c, bottom). We have recently reported that in the course of the heteroarylation of 1,2-dihalobenzenes by thiophenes, a partial Pd 1,4-migration occurred12,13 in some cases, leading to a mixture of 1,2-diheteroarylated benzenes and also to aryl-substituted bilheteroarenes such as 2′-aryl-2,3′-bithiophenes.14 This Pd 1,4-migration on thiophene derivatives provides an appealing method for functionalizing the C–H bonds at the β-position of thiophenes which are often more difficult to activate than those at the α-position.15 In addition, so far, the preparation of 2′-aryl-2,3′-bithiophene derivatives requires multi-step synthesis and the substrate scope is very limited.16 Therefore, the potential of Pd-catalyzed 1,4-migration associated with direct arylation for the access to 2-aryl-3-heteroaryltiophenes via double C–H bond functionalization needed to be explored. Herein, we report (i) on the regioselectivity of the Pd-catalyzed direct arylations vs. Suzuki couplings of 2-(2-bromoaryl)thiophenes and on the scope of the Pd-catalyzed 1,4-migration associated with direct arylation for the formation of 2-aryl-3-heteroaryltiophenes via double C–H bond functionalization (Scheme 1c).
Research Article

Organic Chemistry Frontiers

Results and discussion

First, we prepared a set of 2-(2-bromoaryl)thiophenes via Suzuki coupling or base deprotonation (Scheme 2). All the desired products 1a–1g were obtained in good yields.

Then, we evaluated the selectivity for the Pd-catalyzed coupling of 2-(2-bromophenyl)-5-methylthiophene 1a with 2-acetylthiophene (Table 1). The best yield of the desired isomer 2b arising from the Pd-catalyzed 1,4-migration associated with direct arylation was obtained using 2 mol% Pd(OAc)2 catalyst, whereas xylene and diethyl carbonate (DEC) were ineffective (Table 1, entries 8–11). Finally, a lower reaction temperature of 130 °C instead of 150 °C gave 2b in only 53% yield due to partial conversion of 2-(2-bromoaryl)-5-methylthiophene 1a (Table 1, entry 12). It should be mentioned that this methodology is limited to the use of 2-(2-bromoaryl)thiophenes, as from 3-(2-bromoaryl)thiophenes, complex mixtures of products were obtained.

Next, the scope of this reaction using several heteroarenes and 2-(2-bromoaryl)thiophenes was investigated (Scheme 3). Using 2-isopropylthiazole and 1a, a similar a:b ratio was obtained and product 3b arising from the Pd 1,4-migration was isolated in 65% yield. 2-(2-Bromophenyl)-5-hexylthiophene 1b in the presence of 2-acetylthiophene or cyclopropyl-2-thienylketone afforded products 4b and 5b in 57% and 61% yields, respectively. No side-reaction on the cyclopropyl unit was detected in the course of this reaction. Then, the heteroarylthiophenes 4b and 5b were isolated in 69% and 71% yields, respectively. No cleavage of the thienyl C–Cl bond was observed allowing further transformations. In the presence of selenophene, 1c gave a lower yield of 52% of 6b due to the for-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Base</th>
<th>Conv. (%)</th>
<th>Ratio 2a:2b</th>
<th>Yield in 2b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>KOAc</td>
<td>100</td>
<td>20:80</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>Cs2CO3</td>
<td>5</td>
<td>56:44</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>K2CO3</td>
<td>100</td>
<td>46:54</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>NaOAc</td>
<td>47</td>
<td>19:81</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>CsOAc</td>
<td>84</td>
<td>40:60</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>KOAc</td>
<td>100</td>
<td>24:76</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>PdCl(C3H5)(dppb)</td>
<td>DMA</td>
<td>KOAc</td>
<td>100</td>
<td>24:76</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)2</td>
<td>DMF</td>
<td>KOAc</td>
<td>100</td>
<td>24:76</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)2</td>
<td>NMP</td>
<td>KOAc</td>
<td>100</td>
<td>24:76</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)2</td>
<td>Xylene</td>
<td>KOAc</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)2</td>
<td>DEC</td>
<td>KOAc</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)2</td>
<td>DMA</td>
<td>KOAc</td>
<td>86</td>
<td>20:80</td>
<td>53</td>
</tr>
</tbody>
</table>

Table 1 Influence of the reaction conditions on the Pd-catalyzed coupling of 2-(2-bromophenyl)-5-methylthiophene 1a with 2-acetylthiophene

*Pd* (0.02 equiv.), 2-acetylthiophene (2 equiv.), 2-(2-bromophenyl)-5-methylthiophene 1a (1 equiv.), base (3 equiv.), 150 °C, 16 h, 2a:2b ratios, determined by 1H NMR and GC/MS analyses of the crude mixtures, isolated yields. 130 °C.
formation of unidentified side-products. 2-Isopropyl-4-methyl-thiazole, imidazo[1,2-a]pyrazine and 3,5-dimethylisoxazole in the presence of 1c afforded the target Pd 1,4-migration products 9b–11b in 35–65% yields. These three reactions were performed at a lower temperature of 130 °C due to a partial C–Cl bond cleavage at 150 °C. The reaction also tolerated the presence of two methyl substituents on the benzene ring, however, with this more electron-rich 2-arylthiophene derivative 1e, 5 mol% PdCl(C₅H₆)(dpbb) catalyst had to be employed to reach a high conversion. With this catalyst, the target products 12b and 13b were obtained in 74% and 59% yields, respectively using 2-butylfuran and imidazo[1,2-a]pyrazine as the reaction partners. The reaction also tolerated a 2-acetyl substituent on the thiophen ring. From 2-acetyl-5-arylthiophene 1h and thiophene, furan and thiazole derivatives as reaction partners, very high selectivities (88–94%) of isomers b were observed and the target products 14b–16b were obtained in 72–81% yields. Finally, the reaction of the 2-formyl-5-arylthiophene derivative 1g and 2-methylthiophene or 2-isobutyl-thiazole gave products 17b and 18b with 95% and 87% selectivity and in 68% and 57% yields, respectively.

The use of Pd-catalyzed 1,4-migration associated with direct arylation should allow the introduction of an heteroarene regioselectively at one of the two β-positions of the thiophen ring of non-symmetrical 2,5-diarylthiophenes. The heteroarylation should occur at the β-C–H bond on the same side of the thiophen ring bearing the 2-bromoaryl substituent. The starting materials 19–23 were prepared in 74–86% yields by Pd-catalyzed direct C5-arylation from 2-(2-bromoaryl)thiophene 1d and a set of aryl bromides using the Pd(OAc)₂ catalyst with the KOAc base in DMA (Scheme 4). Under these conditions – slight excess (1.3 equiv.) of an electron-poor aryl halide as the reaction partner – no cleavage of the C–Br bond of the bromotoluene unit of 1d was observed.

Then, the regioselectivity of the direct heteroarylation of 2,5-diarylthiophenes 19–23 was studied (Scheme 5). From 4-(5-(2-bromophenyl)thiophen-2-yl)benzonitrile 19 and 2-methylthiophene, the C₄-heteroarylated product 24b was regioselectively obtained. The regioselectivity of the coupling reaction was determined by X-ray analysis, which confirms that there was no further Pd-migration after the initial Pd 1,4-migration. The reaction also tolerated furan, selenophene and thiazole derivatives as the reaction partners, affording products 25b–28b in 58–67% yields. From chloro- and propionyl-substituted 2,5-diarylthiophenes 20 and 21, the expected products 29b and 30b were also obtained in high yields. Again, under these conditions, no cleavage of the aryl C–Cl bond was observed allowing further transformations. No significant influence of the position of the nitrile substituent on the benzene ring was observed. Both meta- and ortho-nitrile-substituted 2,5-diarylthiophenes 22 and 23 led to the desired...
products 31b and 32b in similar yields. It should be mentioned that for all these heteroarylations of 2,5-diarylthiophenes 19–23, complete regioselectivities in favor of the formation of products b arising from Pd 1,4-migration were observed. This selectivity could be due to the conformation of 2,5-diarylthiophenes 19–23 which would favor the Pd 1,4-migration.

The synthesis of 2,5-diaryl-4-heteroarylthiophene without the isolation of the first arylation compound was also attempted (Scheme 6). From 2-(2-bromo-4-methylphenyl)thiophene 1d, 3-bromopyridine and 2 mol% Pd(OAc)₂ catalyst, the 2,5-diarylated thiophene derivative was obtained in an impure form via filtration on a plug of silica. Then, 2-isopropyl-4-methylthiazole, 2 mol% Pd(OAc)₂ and K₂CO₃ were added to the crude mixture and heated again at 150 °C for 16 h, affording the desired product 33b in 58% yield.

In order to compare the selectivity of the direct arylation reaction with Suzuki coupling, a few arylation of 2-(2-bromophenyl)-5-methylthiophene 1a and 2-(2-bromophenyl)-5-chlorothiophene 1c using aryllboronic acids as the reaction partners were performed (Scheme 7). Again using 2 mol% Pd(OAc)₂ catalyst and DMA as the solvent, but the K₂CO₃ base instead of a carboxylate base, the formation of the expected 1,2-diheteroaryl-substituted benzene derivatives 2a, 34a and 35a was observed with complete selectivity. It should be mentioned that in the presence of the KOPiv base instead of K₂CO₃, isomer 2a was obtained with 73% selectivity (27% of 2b) and in 52% yield indicating that the presence of a carboxylate base favors the Pd 1,4 migration. The reaction of 1c with 2-thienylboronic acid and the K₂CO₃ base also selectively led to the formation of the expected chloro-substituted 1,2-di(thiophen-2-yl)benzene 36a. Using 1c and (3,5-dimethylisoxazol-4-yl)boronic acid as the reaction partner, product 11a was also obtained with complete selectivity. These results demonstrate that the combination of Pd-catalyzed 1,4 migration reactions associated with direct arylation and Suzuki coupling can be employed as a tool to control regiodivergent heteroarylations.

π-Extended polycyclic heteroaromatics²⁰ have found several applications in the preparation of optoelectronic devices. The topology of the ring fusion and the substituents at their periphery are essential to tune their electronic properties. Therefore, we also attempted to apply the Pd-catalyzed 1,4-
migration associated with direct heteroarylation to the preparation of such products. First, we employed a 4-bromothiophene derivative as a reaction partner with 1a (Scheme 8a). The desired naphtho[1,2-b:3,4-b′]dithiophene 37 was obtained in a moderate yield using an extended reaction time (48 h). Intermediate 38 was also isolated in a low yield in an impure form. We also studied the reaction outcome of 2-(2-bromophenyl)-5-methylthiophene in the absence of the heteroaryl coupling partner (Scheme 8b). The formation of the desired fused polyheteroaromatic naphtho[1,2-b:3,4-c′]dithiophene 39 in 65% yield was observed. The structure of 39 was confirmed by X-ray analysis. The formation of 39 likely proceeded via the initial formation of 2-(2-bromophenyl)-2′-phenyl-3,3′-bithiophene. Then, an intramolecular Pd-catalyzed direct arylation gives 1,2-bis(heteroaryl)benzenes. 21

The access to 1,2-bis(heteroaryl)benzenes a proceeds certainly via a classical Suzuki coupling mechanism, whereas the access to 2′-aryl-2,3′-biheteroarenes b occurs likely via a Pd 1,4-migration followed by a direct arylation as described in Scheme 9. In both cases, the first step of the catalytic cycle involves the oxidative addition of 2-(2-bromoaryl)thiophene to give intermediate A. For Suzuki coupling with arylboronic acids, classical transmetalation followed by reductive elimination gives 1,2-bis(heteroaryl)benzenes a. By contrast, with simple heteroarenes using the KOAc base, a Pd 1,4-migration occurs to give intermediate B. Then, after a concerted metalla-deprotonation (CMD)23 of the heteroarene coupling partner, intermediate C is obtained. Finally, reductive elimination provides 2′-aryl-2,3′-biheteroarenes b with the regeneration of the catalyst.

Conclusions

In summary, the use of either Pd-catalyzed 1,4-migration/direct arylation or Suzuki coupling allowed the regiodivergent heteroarylation of 2-(2-bromoaryl)thiophenes. Using Suzuki coupling, 1,2-diheteroarylbenzenes were obtained. Conversely, the use of C–H heteroarylation conditions led to 2-aryl-3-heteroaryldihydrothiophenes due to a Pd 1,4-migration between the aryl and β-position of the thiophene units before heteroarylation. In the course of this coupling reaction, a new C–C bond arises from the functionalization of two C–H bonds. In addition to the advantage of being able to synthesize two classes of products from the same molecular building block, heteroarylation at the β-position of thiophenes by this method is synthetically very attractive because very few β-bromothiophenes, which could allow access to the same products by a classical direct arylation, are commercially available at an affordable cost. The reaction tolerates a variety of heteroarenes and substituents at the C5-position on 2-(2-bromoaryl)thiophenes and provides a new route to π-extended polycyclic heteroaromatics. Moreover, these reactions employ a low loading of air stable palladium sources associated with inexpensive bases. Indeed, we believe that the development of this methodology using other coupling partners for regiodivergent couplings will lead to a powerful tool for organic synthesis.

Experimental

General

DMA (99+%) extra pure and KOAc (99%) were purchased from ACROS and used without purification. All reagents were
weighed and handled in air. All reactions were carried out under an inert atmosphere with standard Schlenk techniques.

1H, 13C and 19F NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. High-resolution mass spectra were measured on a Bruker MaXis 4G spectrometer. Melting points were determined with a Kofer hot bench system. Chromatography purifications were performed using a CombiFlash NextGen 300 with Buchi FlashPure cartridges containing 40 µm irregular silica.

Preparation of the PdCl(C3H5)(dppb) catalyst

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under an argon atmosphere was charged with [Pd(C3H5)Cl]2 (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane was added, and then the solution was stirred at room temperature for twenty minutes. The solvent was removed under vacuum. The yellow powder was used without purification. 31P NMR (162 MHz, CDCl3) δ = 19.3 (s).

General procedures for the preparation of 2-(bromobenzy) thiophenes 1a–1g

Procedure a: As a typical experiment, a mixture of the 1,2-dihalobenzene derivative (3 mmol), the thiophen-2-ylboronic acid derivative (4.5 mmol), 2.0 M K2CO3 aq. (3.6 mL), Pd(OAc)2 (3 mmol), the thiophen-2-ylboronic acid (4.5 mmol), 2.0 M K2CO3 aq. (3.6 mL), Pd(OAc)2 (3 mmol), and dppf (83.1 mg, 0.15 mmol) in THF (20 mL) was stirred at room temperature for twenty minutes. The residue was purified by column chromatography on silica gel to give 2-(2-bromoaryl)thiophenes.

Procedure b: As a typical experiment, to a solution of the 1,2-diha halobenzene derivative (3 mmol), 2.0 M K2CO3 aq. (3.6 mL), Pd(OAc)2 (3 mmol), and dppf (83.1 mg, 0.15 mmol) in THF (20 mL) was added dropwise (1.55 M in hexane, 7.70 mL, 12.0 mmol) at 0 °C. After being stirred for 1 h, the 1,2-dihalobenzene derivative (10.0 mmol) was added to the solution at the same temperature. Then, the mixture was warmed to room temperature and stirred for 2 h. The residue was purified by column chromatography on silica gel to afford 2-(bromomethoxy)thiophenes.

2-(2-Benzyl-5-methylthiophene (1a). Following procedure b, from 1,2-dibromobenzene (2.36 g, 10 mmol) and 2-methylthiophene (1.18 g, 12 mmol), 1a was isolated in 67% (1.69 g) yield as a colorless oil. Eluent pentane.

1H NMR (400 MHz, CDCl3): δ 7.68 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 7.8 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.21–7.12 (m, 2H), 6.81 (d, J = 3.5 Hz, 1H), 2.88 (t, J = 7.4 Hz, 2H), 1.84–1.69 (m, 2H), 1.52–1.29 (m, 6H), 0.95 (t, J = 7.4 Hz, 3H).

13C NMR (100 MHz, CDCl3): δ 147.1, 139.1, 135.8, 133.8, 131.8, 128.7, 127.6, 127.4, 124.1, 123.7, 31.7 (m), 30.3, 29.0, 22.7, 14.2.


2-(2-Benzyl-5-chlorothiophene (1c). Following procedure b, from 1,2-dibromobenzene (2.36 g, 10 mmol) and 2-chlorothiophene (1.42 g, 12 mmol), 1c was isolated in 66% (1.80 g) yield as a yellow oil. Eluent pentane.

1H NMR (400 MHz, CDCl3): δ 7.67 (dd, J = 8.0, 1.3 Hz, 1H), 7.43 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (td, J = 7.6, 1.3 Hz, 1H), 7.19 (td, J = 7.7, 1.7 Hz, 1H), 7.06 (d, J = 3.8 Hz, 1H), 6.93 (d, J = 3.8 Hz, 1H).

13C NMR (100 MHz, CDCl3): δ 140.4, 134.6, 133.9, 131.8, 130.7, 129.5, 127.7, 127.2, 126.2, 122.8.


2-(2-Benzyl-5-bromothiophene (1d). Following procedure a, from 1,2-dibromobenzene (0.891 g, 3 mmol) and 2-thienylboronic acid (0.576 g, 4.5 mmol), 1d was isolated in 62% (0.471 g) yield as a colorless oil. Eluent pentane.

1H NMR (400 MHz, CDCl3): δ 7.51 (s, 1H), 7.39–7.34 (m, 2H), 7.27 (dd, J = 5.6, 1.2 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.10 (dd, J = 5.2, 3.6 Hz, 1H), 2.36 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 142.0, 139.5, 134.2, 132.5, 131.8, 128.4, 127.6, 127.0, 125.9, 122.7, 20.9.


2-(2-Benzyl-5-methylthiophene (1e). Following procedure b, from 1,2-dibromo-4,5-dimethylbenzene (2.64 g, 10 mmol) and 2-methylthiophene (1.18 g, 12 mmol), 1e was isolated in 63% (1.77 g) yield as a colorless oil. Eluent pentane.

1H NMR (400 MHz, CDCl3): δ 7.47 (s, 1H), 7.27 (s, 1H), 7.11 (d, J = 3.5 Hz, 1H), 6.79 (d, J = 3.5 Hz, 1H), 2.57 (s, 3H), 2.29 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 140.3, 139.6, 137.8, 136.1, 134.4, 132.8, 132.7, 127.4, 125.3, 119.2, 19.3, 19.2, 15.4.


5-(2-Benzyl-4-methylthiophen-2-yl)ethan-1-one (1f). Following procedure a, from 2-bromo-1-iodo-4-methylbenzene (0.891 g, 3 mmol) and 2-thienylboronic acid (0.576 g, 4.5 mmol), 1f was isolated in 60% (0.531 g) yield as a yellow oil. Eluent pentane/EtOAc 95/5.

1H NMR (400 MHz, CDCl3): δ 7.65 (d, J = 3.5 Hz, 1H), 7.51 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 2.57 (s, 3H), 2.36 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 190.8, 150.4, 144.2, 140.7, 134.5, 132.3, 131.5, 131.4, 128.7, 128.6, 122.3, 26.8, 20.9.


5-(2-Benzyl-4-methylthiophen-2-yl)ethan-1-one (1g). Following procedure a, from 2-bromo-1-iodo-4-methylbenzene (0.891 g, 3 mmol) and 5-formyl-2-thienylboronic acid (0.702 g, 4.5 mmol), 1g was isolated in 64% (0.539 g) yield as a colorless oil. Eluent pentane/EtOAc 95/5.
General procedure for the preparation of 2-aryl-2,3′-biheteroarenes 2b–18b

As a typical example, the reaction of the 2-(2-bromoaryl) thiophene derivatives 1a–1g (1 mmol), heteroarene (2 mmol) and KOAc (0.294 g, 3 mmol) at 150 °C for 16 h in DMA (4 mL) in the presence of Pd(OAc)2 (4.5 mg, 0.02 mmol) under argon afforded the coupling product after evaporation of the solvent and purification on silica gel. The a:b ratios were determined by 1H NMR and GC/MS analyses of the crude mixtures.

1-(5′-Methyl-2′-phenyl-[2,3′-bithiophen]-5′-yl)-ethan-1-one (2b).
From 2-(2-bromophenyl)-5-methylthiophene 1a (0.253 g, 1 mmol) and 2-acetyltetrahydrofuran (0.252 g, 2 mmol), a mixture of 2a and 2b was obtained in a 19:81 ratio and 2b was isolated in 64% (0.191 g) yield as a white solid: mp 92–94 °C. Eluent pentane, Rf 2a = 0.30, Rf 2b = 0.33.

1H NMR (400 MHz, CDCl3): δ 7.46 (d, J = 3.9 Hz, 1H), 7.40–7.32 (m, 5H), 6.91 (s, 1H), 6.79 (d, J = 3.9 Hz, 1H), 2.51 (s, 3H), 2.49 (s, 3H).
13C NMR (100 MHz, CDCl3): δ 190.6, 147.6, 145.6, 142.5, 183.0, 151.9, 143.6, 133.1, 132.5, 129.9, 128.7, 128.2, 127.6, 127.5, 42.4, 29.8, 22.4, 15.3.

2-Isobutyl-5-(5-methyl-2-phenylthiophen-3-yl)thiazole (3b).
From 2-(2-bromophenyl)-5-methylthiophene 1a (0.253 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), a mixture of 3a and 3b was obtained in a 20:80 ratio and 3b was isolated in 65% (0.203 g) yield as a colorless oil. Eluent pentane, Rf 3a = 0.20, Rf 3b = 0.23.

1H NMR (400 MHz, CDCl3): δ 7.47 (s, 1H), 7.39–7.30 (m, 5H), 6.86 (s, 1H), 2.77 (d, J = 7.6 Hz, 2H), 2.50 (s, 3H), 2.09–1.99 (m, 1H), 0.95 (d, J = 7.6 Hz, 6H).
13C NMR (100 MHz, CDCl3): δ 169.5, 139.9, 139.1, 137.5, 133.9, 132.5, 129.9, 128.7, 128.2, 127.6, 127.5, 42.4, 29.8, 22.4, 15.3.

Cyclopropyl[5′-hexyl-2′-phenyl-[2,3′-bithiophen]-5′-yl]methanone (5b).
From 2-(2-bromophenyl)-5-hexylthiophene 1b (0.233 g, 1 mmol) and cyclopropyl[thiophen-2-yl]methanone (0.304 g, 2 mmol), a mixture of 5a and 5b was obtained in a 20:80 ratio and 5b was isolated in 61% (0.240 g) yield as a yellow oil. Eluent pentane/EtOAc 80/20, Rf 5a = 0.29, Rf 5b = 0.33.

1H NMR (400 MHz, CDCl3): δ 7.59 (d, J = 4.0 Hz, 1H), 7.42–7.32 (m, 3H), 6.93 (s, 1H), 6.83 (d, J = 4.0 Hz, 1H), 2.81 (t, J = 7.6 Hz, 2H), 2.50–2.39 (m, 1H), 1.72 (quint, J = 7.6 Hz, 2H), 1.49–1.38 (m, 2H), 1.38–1.28 (m, 4H), 1.25–1.18 (m, 2H), 1.02–0.95 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H).
13C NMR (100 MHz, CDCl3): δ 192.8, 147.0, 145.5, 143.0, 138.3, 134.0, 131.9, 129.8, 129.6, 128.8, 128.3, 126.6, 126.4, 31.7, 31.6, 30.1, 29.0, 22.7, 17.9, 14.2, 11.3.

5-Chloro-5-methyl-2-phenyl-2′,3′-bithiophene (6b).
From 2-(2-bromophenyl)-5-chlorothiophene 1c (0.273 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol), a mixture of 6a and 6b was obtained in a 9:91 ratio and 6b was isolated in 69% (0.201 g) yield as a colorless oil. Eluent pentane, Rf 6a = 0.30, Rf 6b = 0.33.
1H NMR (400 MHz, CDCl3): δ 7.42–7.31 (m, 5H), 7.01 (s, 1H), 6.66 (d, J = 3.5 Hz, 1H), 6.55 (d, J = 3.5 Hz, 1H), 2.41 (s, 3H).
13C NMR (100 MHz, CDCl3): δ 139.9, 136.2, 135.0, 133.3, 130.8, 130.0, 128.8, 128.5, 128.4, 126.1, 125.5, 15.4.

2-(5′-Chloro-2′-phenyl-[2,3′-bithiophen]-5′-yl)-2-methyl-1,3-dioxolane (7b).
From 2-(2-bromophenyl)-5-chlorothiophene 1c (0.273 g, 1 mmol) and 2-methyl-(thiophen-2-yl)-1,3-dioxolane (0.340 g, 2 mmol), a mixture of 7a and 7b was obtained in a 9:91 ratio and 7b was isolated in 71% (0.257 g) yield as a yellow solid: mp 128–130 °C. Eluent pentane/EtOAc 80/20, Rf 7a = 0.23, Rf 7b = 0.27.
1H NMR (400 MHz, CDCl3): δ 7.40–7.31 (m, 5H), 7.02 (s, 1H), 6.82 (d, J = 3.7 Hz, 1H), 6.67 (d, J = 3.7 Hz, 1H), 4.05–3.98 (m, 2H), 3.98–3.91 (m, 2H), 1.74 (s, 3H).
13C NMR (100 MHz, CDCl3): δ 147.0, 137.0, 136.9, 133.1, 130.3, 129.9, 129.0, 128.8, 128.6, 128.4, 125.9, 124.4, 107.2, 65.1, 27.5.

5-Chloro-2-phenyl-3-(selenophen-2-yl)thiophene (8b).
From 2-(2-bromophenyl)-5-chlorothiophene 1c (0.273 g, 1 mmol) and selenophene (0.262 g, 2 mmol), a mixture of 8a and 8b was obtained in a 20:80 ratio and 11b was isolated in 52% (0.168 g) yield as a colorless oil. Eluent pentane, Rf 8a = 0.29, Rf 8b = 0.33.
1H NMR (400 MHz, CDCl3): δ 7.85 (dd, J = 5.6, 1.2 Hz, 1H), 7.43–7.36 (m, 5H), 7.15 (dd, J = 5.6, 3.8 Hz, 1H), 7.11 (dd, J = 3.8, 1.2 Hz, 1H), 7.06 (s, 1H).
13C NMR (100 MHz, CDCl3): δ 142.7, 136.6, 133.0, 132.8, 131.0, 130.3, 129.6, 128.9, 128.8, 128.5, 128.3.
1H NMR (400 MHz, CDCl3): δ 7.31–7.15 (m, 5H), 6.89 (s, 1H), 3.23 (sept., J = 7.6 Hz, 1H), 2.01 (s, 3H), 1.37 (d, J = 7.6 Hz, 6H).


From 1-(5-Methyl-2-tolyl)-[2,3-bithiophen]-3'-ylyl)ethan-1-one (14b).
From 1-(5-bromo-4-methylphenyl)thiophen-2-yl)ethan-1-one (16b).

Organic Chemistry Frontiers

Research Article

(0.282 g, 2 mmol), a mixture of 16a and 16b was obtained in a 12:88 ratio and 16b was isolated in 58% (0.256 g) yield as a yellow solid: mp 87–89 °C. Eluent pentane/EtOAc 80/20, Rf 16a = 0.20, Rf 16b = 0.23.

1H NMR (400 MHz, CDCl3): δ 7.71 (s, 1H), 7.51 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.80 (d, J = 7.6 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 2.10–2.02 (m, 1H), 0.96 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 190.5, 170.4, 148.4, 142.3, 140.6, 139.6, 134.2, 131.1, 129.7, 129.6, 129.4, 128.7, 42.4, 29.8, 26.7, 22.3, 21.5.

HRMS calcld for [M + H]⁺ C26H22N2O6S 356.1137, found: 356.1136.

5-Methyl-2-(p-toly)-[2,3’-bithiophene]-5’-carbaldehyde (17b). From 5-(2-bromo-4-methylphenyl)thiophene-2-carbaldehyde 1g (0.281 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol), a mixture of 17a and 17b was obtained in a 5:95 ratio and 17b was isolated in 68% (0.203 g) yield as a yellow oil. Eluent pentane/EtOAc 80/20, Rf 17a = 0.23, Rf 17b = 0.27.

1H NMR (400 MHz, CDCl3): δ 9.88 (s, 1H), 7.79 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 3.5 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 182.9, 148.2, 141.2, 140.4, 139.5, 138.4, 134.4, 132.6, 130.2, 129.6, 129.4, 126.5, 125.6, 21.5, 15.4.

HRMS calcld for [M + H]⁺ C17H15OS2 356.0959, found: 356.0957.

4-(2-Isobutylthiazol-5-yl)-5-(p-toly)thiophene-2-carbaldehyde (18b). From 5-(2-bromo-4-methylphenyl)thiophene-2-carbaldehyde 1g (0.281 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), a mixture of 18a and 18b was obtained in a 13:87 ratio and 18b was isolated in 57% (0.194 g) yield as a yellow solid: mp 90–92 °C. Eluent pentane/EtOAc 80/20, Rf 18a = 0.10, Rf 18b = 0.12.

1H NMR (400 MHz, CDCl3): δ 9.90 (s, 1H), 7.80 (s, 1H), 7.53 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 2.80 (d, J = 7.6 Hz, 2H), 2.39 (s, 3H), 2.10–2.02 (m, 1H), 0.97 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 182.7, 170.6, 149.8, 141.6, 140.8, 140.0, 138.0, 129.7, 129.5, 129.4, 129.1, 42.4, 29.8, 22.3, 21.5.


1H NMR (400 MHz, CDCl3): δ 7.55 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.29–7.23 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 2.38 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 143.4, 141.7, 139.6, 134.3, 133.4, 132.9, 132.1, 131.5, 129.2, 128.7, 128.5, 127.0, 123.4, 122.4, 20.8.


5-(2-Bromo-4-methylphenyl)thiophene (20). From 2-(2-bromo-4-methylphenyl)thiophene 1d (0.253 g, 1 mmol) and 1-bromo-4-chlorobenzene (0.249 g, 1.3 mmol), 20 was isolated in 74% (0.269 g) yield as a yellow oil. Eluent pentane/EtOAc 95/5.

General procedure for the preparation of 2,5-diarylthiophenes 19–23

As a typical experiment, the reaction of 2-(2-bromo-4-methylphenyl)thiophene 1d (0.253 g, 1 mmol), aryl bromide (1.3 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C for 16 h in DMA (4 mL) in the presence of Pd(OAc)₂ (4.5 mg, 0.02 mmol) under argon afforded the coupling product after evaporation of the solvent and purification on silica gel.

4-(2-Bromomethyl)thiophen-2-yl)benzonitrile (19). From 2-(2-bromo-4-methylphenyl)thiophene 1d (0.253 g, 1 mmol) and 4-bromobenzonitrile (0.237 g, 1.3 mmol), 19 was isolated in 85% (0.301 g) yield as a yellow oil. Eluent pentane/EtOAc 95/5.

H NMR (400 MHz, CDCl3): δ 7.68 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.52 (s, 1H), 7.40–7.36 (m, 2H), 7.28 (d, J = 3.7 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 2.36 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 143.6, 142.1, 140.0, 138.5, 134.4, 132.8, 131.6, 131.4, 129.0, 128.5, 125.9, 125.1, 122.3, 118.9, 110.6, 20.8.


This journal is © the Partner Organisations 2023.

Org. Chem. Front., 2023, 10, 1441-1455 | 1449
General procedure for the preparation of heteroarylated 2,3-diaryltiophenes 24b–32b

As a typical experiment, the reaction of the 2-(2-bromophenyl)-5-arylthiophene derivative 19–23 (1 mmol), heteroarene (0.196 g, 2 mmol), and 2-methylthiophene (0.262 g, 2 mmol) in DMA (4 mL) in the presence of Pd(OAc)2 (4.5 mg, 0.02 mmol) under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

4-(5-Methyl-2-(p-tolyl)-2,3-bithiophen)-5’-ylbenzonitrile (24b). From 4-(5-(2-bromophenyl)-thieno-2-yl)benzonitrile 19 (0.340 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol), 24b was isolated in 71% (0.263 g) yield as a yellow solid: mp 144–146 °C. Eluent pentane/EtOAc 80/20, Rf = 0.30.

1H NMR (400 MHz, CDCl3): δ 7.69 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.45 (s, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.74 (d, J = 3.5 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 2.45 (s, 3H), 2.40 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 133.3, 130.1, 128.4, 123.9, 132.5, 130.6, 129.6, 129.5, 127.6, 125.8, 125.9, 119.6, 110.9, 21.5, 21.4.


4-(4-(2-Isopropyl-4-methylthiazol-5-yl)-5-(p-tolyl)thieno-2-yl)benzonitrile (27b). From 4-[5-(2-bromophenyl)thieno-2-yl]benzonitrile 19 (0.340 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.282 g, 2 mmol), 27b was isolated in 63% (0.261 g) yield as a white solid: mp 144–146 °C. Eluent pentane/EtOAc 80/20, Rf = 0.17.

1H NMR (400 MHz, CDCl3): δ 7.70 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.35 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 3.26 (sept, J = 7.6 Hz, 1H), 2.35 (s, 3H), 2.04 (s, 3H), 1.40 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 176.7, 148.9, 143.4, 139.6, 138.4, 138.2, 132.9, 130.6, 129.7, 129.3, 128.9, 128.2, 125.8, 124.2, 118.9, 110.9, 33.5, 23.3, 21.4, 15.9.


4-(4-(2-Isobutylthiazol-5-yl)-5-(p-tolyl)thieno-2-yl)benzonitrile (28b). From 4-[5-(2-bromophenyl)thieno-2-yl]benzonitrile 19 (0.340 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), 28b was isolated in 66% (0.274 g) yield as a yellow solid: mp 140–142 °C. Eluent pentane/EtOAc 80/20, Rf = 0.23.

1H NMR (400 MHz, CDCl3): δ 7.71 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.55 (s, 1H), 7.47 (s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 2.80 (d, J = 7.6 Hz, 2H), 2.40 (s, 3H), 2.11–2.03 (m, 1H), 0.97 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 170.2, 141.7, 140.4, 140.3, 139.1, 138.13, 130.0, 131.0, 129.6, 129.5, 129.0, 127.3, 125.9, 118.9, 111.1, 42.5, 29.9, 22.4, 21.5.


5-(4-Chlorophenyl)-2-(p-tolyl)thiophen-3-yl)-2-isopropyl-4-methylthiazole (29b). From 2-(2-bromo-4-methylphenyl)-5-(4-chlorophenyl)thiophene 20 (0.350 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.282 g, 2 mmol), 29b was isolated in 74% (0.314 g) yield as a yellow solid: mp 90–92 °C. Eluent pentane/EtOAc 80/20, Rf = 0.20.

1H NMR (400 MHz, CDCl3): δ 7.54 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.22 (s, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 3.26 (sept, J = 7.6 Hz, 1H), 2.34 (s, 3H), 2.04 (s, 3H), 1.40 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 176.5, 148.7, 141.5, 140.8, 138.0, 133.7, 132.5, 131.0, 129.6, 129.3, 128.4, 128.2, 127.6, 126.9, 124.7, 33.5, 23.3, 21.4, 15.9.


1-(4-(4-(2-Isopropyl-4-methylthiazol-5-yl)-5-(p-tolyl)thieno-2-yl)phenyl)propan-1-one (30b). From 1-(4-[5-(2-bromo-4-methylphenyl)thieno-2-yl]phenyl)propan-1-one 21 (0.371 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.282 g, 2 mmol), 30b was isolated in 73% (0.325 g) yield as a yellow solid: mp 120–122 °C. Eluent pentane/EtOAc 80/20, Rf = 0.27.

1H NMR (400 MHz, CDCl3): δ 7.99 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.36 (s, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 3.27 (sept, J = 7.6 Hz, 1H), 3.02 (q, J = 7.6 Hz, 2H), 2.35 (s, 3H), 2.05 (s, 3H), 1.40 (d, J = 7.6 Hz, 6H), 1.25 (t, J = 7.6 Hz, 3H).
13C NMR (100 MHz, CDCl3): δ 201.1, 176.6, 148.9, 142.7, 140.6, 138.2, 138.1, 135.9, 130.9, 129.6, 129.0, 128.7, 128.3, 125.5, 124.5, 33.6, 31.9, 23.3, 21.4, 15.9, 8.5.

HRMS calex for [M + H]+ C27H28NOS2 446.1607, found: 446.1608.

3-(4-(2-Isopropyl-4-methylthiazol-5-yl)-5-(p-tolyliothien-2-yl)benzonitrile (31b). From 3-(5-(2-bromophenyl)thiophen-2-yl)benzonitrile (0.282 g, 2 mmol), and KOAc (0.294 g, 3 mmol) at 130 °C. Eluent pentane/EtOAc 80/20, Rf = 0.23.

1H NMR (400 MHz, CDCl3): δ 7.88 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.30 (s, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 3.27 (sept., J = 7.6 Hz, 1H), 2.35 (s, 3H), 2.04 (s, 3H), 1.40 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 176.7, 148.9, 142.7, 139.2, 138.3, 135.3, 130.9, 130.6, 129.7, 129.6, 129.0, 128.7, 128.6, 128.3, 124.3, 118.5, 33.5, 23.3, 21.4, 15.9.

HRMS calex for [M + H]+ C27H28NOS2 446.1607, found: 446.1608.

2-(5-(2-bromophenyl)thiophen-2-yl)bromobenzene (32b). From 2-(5-(2-bromophenyl)thiophen-2-yl)bromobenzene (0.340 g, 2 mmol), and 2-isopropyl-4-methyl-thiazole (0.282 g, 2 mmol) at 130 °C. Eluent pentane/EtOAc 80/20, Rf = 0.30.

1H NMR (400 MHz, CDCl3): δ 7.75 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 3.26 (sept., J = 7.6 Hz, 1H), 2.34 (s, 3H), 2.12 (s, 3H), 1.39 (d, J = 7.6 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 176.6, 149.0, 143.6, 138.3, 137.2, 137.1, 134.6, 133.2, 131.5, 130.5, 129.6, 129.4, 128.6, 128.5, 127.8, 124.2, 118.9, 109.9, 33.5, 23.3, 21.4, 15.9.

HRMS calex for [M + H]+ C27H28NOS2 446.1607, found: 446.1608.

2-Isothiazol-4-yl(thiophene-2-yl)thiophene (33b). As a typical experiment, the reaction of 2-(2-bromophenyl)thiophene derivative 1 (1 mmol), heteroarylboronic acid (2 mmol) and K2CO3 (0.276 g, 2 mmol) at 150 °C for 16 h in DCM (4 mL) in the presence of Pd(OAc)2 (11.3 mg, 0.05 mmol) under argon afforded the coupling product after evaporation of the solvent and purifcation on silica gel.

1-(5-(2-Methylthiophene-2-yl)phenyl)hiotien-2-yl)methanone (2a). From 2-(2-bromophenyl)-5-methylthiophene 1a (0.253 g, 1 mmol) and (5-acetylthiophen-2-yl)boronic acid (0.340 g, 2 mmol) 2a was obtained in 61% (0.182 g) yield as a yellow oil. Eluent pentane, Rf = 0.30.

1H NMR (400 MHz, CDCl3): δ 7.54 (d, J = 3.9 Hz, 1H), 7.50–7.46 (m, 2H), 7.42–7.32 (m, 2H), 6.88 (d, J = 3.9 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 2.53 (s, 3H), 2.45 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 190.8, 152.0, 144.2, 141.1, 139.6, 134.4, 132.8, 132.6, 131.4, 131.0, 129.0, 128.3, 127.9, 127.4, 125.6, 26.8, 15.5.

HRMS calex for [M + H]+ C16H13OS2 285.0402, found: 285.0400.
2-Chloro-5-(2-thiophen-2-yl)phenylthiophene (36a). From 2-(2-bromomethyl)-5-chlorothiophene 1c (0.271 g, 1 mmol) and 2-thienylboronic acid (0.256 g, 2 mmol), 36a was obtained in 91% (0.252 g) yield as a yellow oil. Eluent pentane, \( R_f = 0.33. \)

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta 7.53-7.43 \) (m, 2H), 7.40-7.33 (m, 2H), 7.31 (dd, \( J = 5.1, 1.2 \) Hz, 1H), 7.00 (dd, \( J = 5.1, 3.5 \) Hz, 1H), 6.93 (dd, \( J = 3.5, 1.2 \) Hz, 1H), 6.77 (d, \( J = 3.8 \) Hz, 1H), 6.68 (d, \( J = 3.8 \) Hz, 1H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta 142.2, 141.5, 133.8, 133.2, 131.4, 130.9, 130.4, 128.4, 128.2, 127.5, 127.2, 126.4, 126.3, 126.2.

HRMS caled for [M + H]\(^{+}\) \( C_{14}H_{10}ClS_2 \): 276.9907, found: 276.9909.

4-(2-(5-Chlorothiophen-2-yl)phenyl)-3,5-dimethylisoazole (11a). From 2-(2-bromomethyl)-5-chlorothiophene 1c (0.271 g, 1 mmol) and (3,5-dimethylisoazole-4-yl)boronic acid (0.282 g, 2 mmol), 11a was obtained in 58% (0.168 g) yield as a yellow oil. Eluent pentane/EtOAc 80/20, \( R_f = 0.30. \)

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta 7.56 \) (d, \( J = 7.8 \) Hz, 1H), 7.43 (t, \( J = 7.6 \) Hz, 1H), 7.37 (t, \( J = 7.6 \) Hz, 1H), 7.20 (d, \( J = 7.8 \) Hz, 1H), 6.78 (d, \( J = 3.8 \) Hz, 1H), 6.69 (d, \( J = 3.8 \) Hz, 1H), 2.18 (s, 3H), 1.95 (s, 3H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta 166.3, 159.5, 140.9, 134.3, 132.1, 130.8, 129.8, 129.0, 128.3, 128.0, 126.4, 125.5, 116.0, 11.4, 10.5.

HRMS caled for [M + H]\(^{+}\) \( C_{13}H_{13}ClS_2 \): 290.0401, found: 290.0402.

5-(4-(2-(5-Chlorothiophen-2-yl)phenyl)-3,5-dimethylisoxazole-4-yl)thiophene (12a). From 2-(2-bromomethyl)-5-chlorothiophene 1c (0.253 g, 1 mmol) and 2,5-dimethylnaphtho[1,2-b]thiophene (40).

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta 8.15 \) (s, 1H), 7.60 (s, 1H), 7.34 (s, 1H), 7.30 (d, \( J = 7.0 \) Hz, 1H), 7.22 (d, \( J = 7.0 \) Hz, 1H), 6.73 (q, \( J = 1.3 \) Hz, 1H), 3.04 (s, 3H), 2.45 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta 137.6, 136.7, 136.6, 135.3, 135.0, 134.7, 132.5, 132.2, 132.0, 130.5, 129.8, 129.8, 128.5, 128.7, 128.5, 128.2, 127.4, 108.9, 15.6, 15.5.

HRMS caled for [M + H]\(^{+}\) \( C_{26}H_{25}S_2 \): 401.1392, found: 401.1393.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

We are grateful to the CSC for a grant to L. L. We thank the CNRS and “Rennes Metropole” for providing financial support.

**References**


4 For selected examples of direct arylation of thiophenes:

5 For selected examples of direct arylation of furans:

6 For selected examples of direct arylation of pyrroles or indoles:

7 For selected examples of direct arylation of thiazoles:


9 For examples of C3-heteroarylations of thiophenes using Suzuki or Stille couplings with 2-aryl-3-halothiophenones:


11 For the preparation of 3-bromothiophenes:


12 For reviews on 1,4-migration of Pd in catalytic organometallic reactions:


13 For selected examples of Pd-catalyzed reactions involving Pd-migration:


15 For examples of Pd-catalyzed direct C3-arylations of thiophene derivatives:


16 For rare examples of synthesis of 2’-aryl-2,3’-bithiophene derivatives:


18 From a mixture of 4-(2-bromophenyl)-2-methylthiophene and 2-methylthiophene or 2-acetylthiophene, under the same conditions, complex mixtures of products were obtained.


