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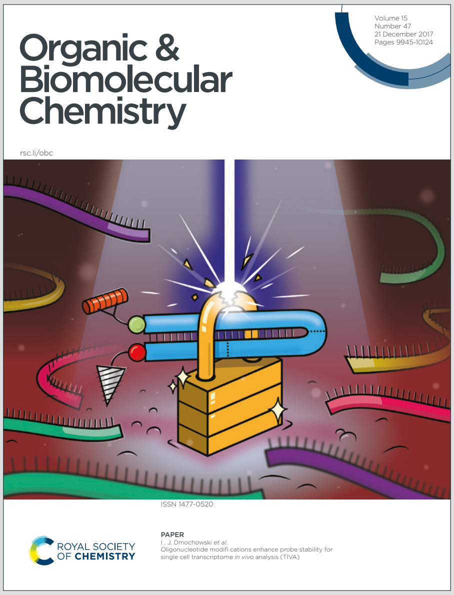

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ARTICLE

Palladium-catalyzed 1,4-Migration for the Regioselective C-H Bond Functionalization at C2-Position of 3-Arylthiophenes

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Abstract: The regioselective functionalization of the C-H bond at the C2-position of 3-substituted thiophenes is challenging, as both thienyl *α*-positions may be reactive, generally affording mixtures of C2-, C5- and C2,C5-(di)functionalized thiophenes. We established that using palladium 1,4-migration allows for the regioselective functionalization of only one of the two *α*-positions of 3-arylthiophenes. The oxidative addition of the 3-(2-bromoaryl)thiophenes to palladium followed by such palladium migration, regioselectively activates the thienyl C2-*α*-position. Next, C2-heteroarylated 3-arylthiophene derivatives can be obtained through palladium-catalyzed direct coupling with heteroarenes. The new C-C bond that this reaction generates comes from the functionalization of two C-H bonds. This thienyl heteroarylation method tolerates a variety of heteroarenes and several substituents on the 3-arylthiophene. In addition, an easily available air-stable catalyst and an inexpensive base were employed for this reaction.

Introduction

Thiophene derivatives bearing a heteroaryl substituent at the C2 position and an aryl group at the C3 position exhibit properties that make them highly attractive for applications in pharmaceutical chemistry,[1-3] including as antitumor agents, as well as in organic electronics, such as solar cells.[4] However, the preparation of such compounds remains a challenging process and necessitates a number of synthetic steps. They are currently generally prepared via palladium-catalyzed Suzuki and Stille cross-coupling reactions, typically from 3-aryl-2-halothiophenes.[5-11] Consequently, the identification of more straightforward methods for their preparation is a significant area of current research.

Catalytic reactions that functionalize specific C-H bonds of organic molecules often result in simple synthetic methods.[12-20] For instance, the Pd-catalyzed C–H bond activation/functionalization of heteroarenes, reported by Ohta et al. in 1990,[21,22] has become one of the most reliable and cost-effective methods for preparing heteroarylated arenes, including thiophenes.[23-26] However, in several cases, due to the similar reactivity of two C-H bonds on some substrates, such Pd-catalyzed C–H bond functionalization led to the formation of mixtures of products.[27] For example, the reaction of 3-phenylthiophene with 4-bromotoluene produced a mixture of C2-, C5-, and C2,C5-(di)arylated thiophenes in a 9:9:70 ratio, even when an equimolar amount of reactants was used (Scheme 1, b).[28] Consequently, the regioselective C2-(hetero)arylation of such 3-arylthiophenes via a C-H bond functionalization remains challenging. This is why synthetic chemists currently rely on more traditional palladium-catalyzed reactions, such as the Suzuki coupling, to synthesize C2-(hetero)arylated 3-arylthiophene derivatives.[6-11]

We recently reported that, during the palladium-catalyzed heteroarylation of 2-(2-bromoaryl)thiophenes with heteroarenes, partial palladium 1,4-migration[29-33] occurred in some cases.[34] The predominant formation of 2-arylthiophenes heteroarylated at the *β*-position of thiophene, such as 2'-aryl-2,3'-bithiophenes, was the result of this Pd-migration, providing a simple method to functionalize such thienyl *β*-C-H bonds. To the best of our knowledge, there has been no report of the C-H bond activation of the thienyl *α*-position via such Pd 1,4-migration. Using Pd 1,4-migration with 3-(2-bromoaryl)thiophenes would enable the regioselective preparation of 2-heteroaryl-3-arylthiophenes in only two steps. This Pd 1,4-migration method is different from the more traditional Pd-catalyzed direct arylation in that it should only activate the thienyl C2-position, not its C5-position (see Scheme 1). Therefore, we investigated the outcome of the reaction of the palladium-catalyzed coupling of 3-(2-bromoaryl)thiophenes with heteroarenes. Herein, we report on 1) the regioselectivity of the Pd-catalyzed direct arylations of 3-(2-bromoaryl)thiophenes, 2) the scope of the reaction using various heteroarenes and 3-(2-bromoaryl)thiophene derivatives (Scheme 1, bottom).

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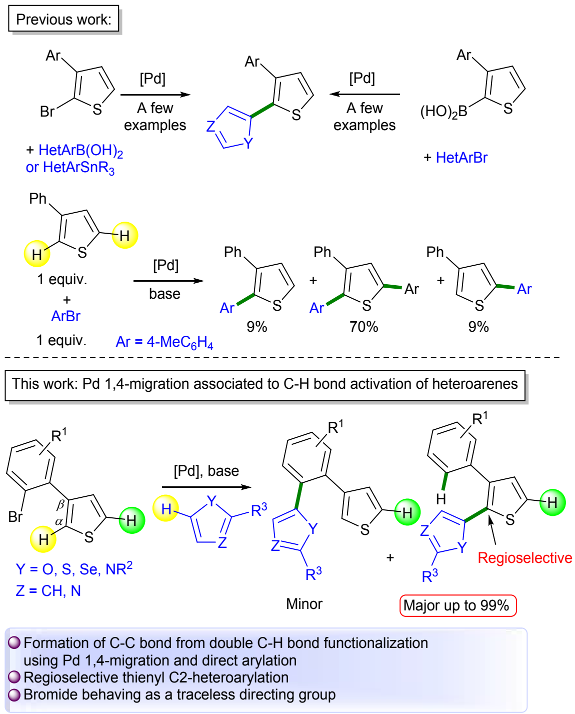
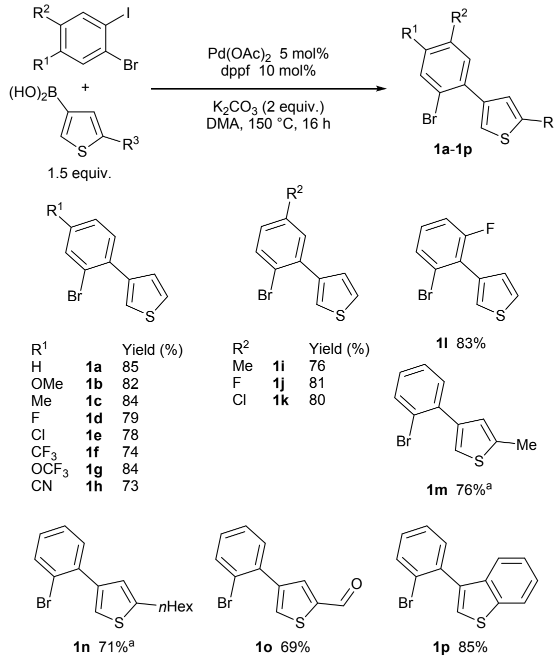


Scheme 1. Pd-catalyzed C2-(hetero)arylations of 3-arylthiophenes; direct arylation *vs* classical cross-couplings.

Results and discussion

First, we synthesized a series of 3-(2-bromoaryl)thiophenes *via* palladium-catalyzed Suzuki (Scheme 2). The expected products **1a**-**1p** were obtained in good yields.



a: For procedure, see ref 36.

Scheme 2. Preparation of the 3-(2-bromoaryl)thiophenes **1a**-**1p**.

Next, we determined the selectivity of the palladium-catalyzed coupling reaction between 3-(2-bromophenyl)thiophene **1a** and 2-ethyl-4-methylthiazole (Table 1).[38-40] Based on our previously reported reaction conditions,[34] using a 5 mol% $Pd(OAc)_2$ catalyst and KOPiv as the base in DMA, the desired product **2b**, arising from Pd-catalyzed 1,4-migration associated with direct arylation, was obtained in 78% selectivity (Table 1, entry 1). In contrast, product **2a**, which arose from the non-migrated palladium intermediate, was obtained in 22% selectivity. The conversion of **1a** was only 63% using this phosphine ligand-free $Pd(OAc)_2$ catalyst. Conversely, complete conversion of **1a** was observed in the presence of the more stable $PdCl(C_3H_5)(dppb)$[37] catalyst (Table 1, entry 2). Furthermore, the ratio of products **2a** and **2b** increased to 5:95, and desired product **2b** was isolated with a yield of 77%. Using acetate bases KOAc and NaOAc gave the product **2b** with slightly lower selectivity and yield than when KOPiv base was employed (Table 1, entries 3 and 4). The Na_2CO_3 base also gave a good selectivity in the desired product **2b**, but a very low conversion of **1a** was observed (Table 1, entry 5). In contrast, the other carbonate bases, Cs_2CO_3 and K_2CO_3, led to poor selectivities in **2a** and **2b** products (Table 1, entries 6 and 7). With these two bases, the product **2a**, resulting from the non-migrated palladium intermediate, was predominant with 60%-65% selectivity. The influence of a few solvents on the reaction outcome was also examined. Reactions performed in DMF and NMP gave the desired product **2b** resulting from Pd 1,4-migration, albeit with slightly lower selectivity than in DMA (Table 1, entries 8 and 9). Conversely, the less polar solvents, xylene and diethyl carbonate (DEC) were ineffective (Table 1, entries 10 and 11). Finally, reducing the reaction temperature to 130 °C (from 150 °C) produced **2b** in 70% yield due to a slightly lower selectivity of the reaction (Table 1, entry 12).

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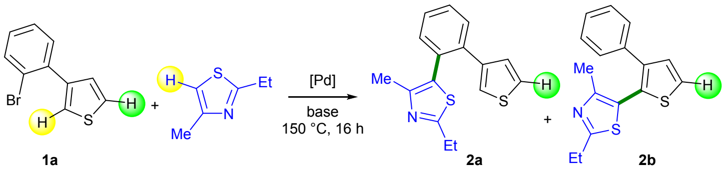
Table 1. Influence of the reaction conditions on the Pd-catalyzed coupling of 3-(2-bromophenyl)thiophene **1a** with 2-ethyl-4-methylthiazole.[a]



Entry	Catalyst	Solvent	Base	Conv. (%)	Ratio **2a**:**2b**	Yield in **2b** (%)
1	$Pd(OAc)_2$	DMA	KOPiv	63	22:78	-
2	$PdCl(C_3H_5)(dppb)$	DMA	KOPiv	100	5:95	77
3	$PdCl(C_3H_5)(dppb)$	DMA	KOAc	99	6:94	75
4	$PdCl(C_3H_5)(dppb)$	DMA	CsOAc	100	11:89	71
5	$PdCl(C_3H_5)(dppb)$	DMA	Na_2CO_3	20	8:92	< 5
6	$PdCl(C_3H_5)(dppb)$	DMA	K_2CO_3	100	60:40	-
7	$PdCl(C_3H_5)(dppb)$	DMA	Cs_2CO_3	100	65:35	41 of **2a**
8	$PdCl(C_3H_5)(dppb)$	DMF	KOPiv	100	9:91	75
9	$PdCl(C_3H_5)(dppb)$	NMP	KOPiv	100	13:87	70
10	$PdCl(C_3H_5)(dppb)$	Xylene	KOPiv	100	Not determined	< 10
11	$PdCl(C_3H_5)(dppb)$	DEC	KOPiv	100	Not determined	< 10
12	$PdCl(C_3H_5)(dppb)$	DMA	KOPiv	100	11:89	70[b]

a) [Pd] (0.05 equiv.), 2-ethyl-4-methylthiazole (2 equiv.), 3-(2-bromophenyl)thiophene **1a** (1 equiv.), base (2 equiv.), 150 °C, 16 h, **2a**:**2b** ratios determined by ^1H NMR and GC/MS analysis of the crude mixtures, isolated yields. b) 130 °C.

Then, we investigated the influence of the substituents on the aryl group of the 3-(2-bromoaryl)thiophene in this reaction, using 2-ethyl-4-methylthiazole as the reaction partner (Scheme 3). Our study began with the examination of the influence of a set of 3-(2-bromoaryl)thiophene compounds with various substituents in the *meta*-position to the C-Br bond on the selectivity. The presence of a methyl substituent slightly increased the selectivity in the desired product **4b** to 96%. Conversely, in the presence of fluorine and chlorine substituents, we obtained lower selectivities of 80% and 73%, respectively, for isomers **5b** and **6b**. These results suggest that the presence of an electron-withdrawing substituent on the aryl unit is less favourable to the palladium 1,4-migration. This trend was confirmed using a 3-arylthiophenes with CF_3 or OCF_3 substituents that were also in the *meta*-position relative to the C-Br bond, which gave isomers **7b** and **8b** with 79% and 76% selectivity, respectively. A nitrile substituent, which is strongly electron-withdrawing, on the aryl unit, was well tolerated, affording product **9b** in 80% selectivity. Then, reactions involving 3-(2-bromoaryl)thiophene with substituents on the aryl in the *para*-position relative to the C-Br bond were performed. Methyl and fluoro substituents (Hammett σp constants of -0.17 and 0.06) furnished the target products **10b** and **11b** in 98% and 96% selectivities, respectively. A chloro *para*-substituent was also well tolerated and produced compound **12b** in 93% selectivity. Therefore, the selectivity of this reaction appears to be influenced by the Hammett constants (σm or σp depending on the position of the aryl substituent relative to the C-Br bond), since low Hammett constants tend to favour Pd 1,4-migration in all cases (Scheme 4). However, kinetic studies would be required to gain more insight into the factors governing the Pd 1,4-migration process. In the presence of 3-(2-bromo-6-fluorophenyl)thiophene **1l**, we also obtained a good selectivity of 87% in desired product **13b**. It should be noted that reaction selectivity also depends on the heteroaryl coupling partner. For example, when we used 2-isobutylthiazole instead of 2-ethyl-4-methylthiazole, we observed a lower selectivity in the Pd-1,4-migration product, affording isomer **14b** with only 77% selectivity.

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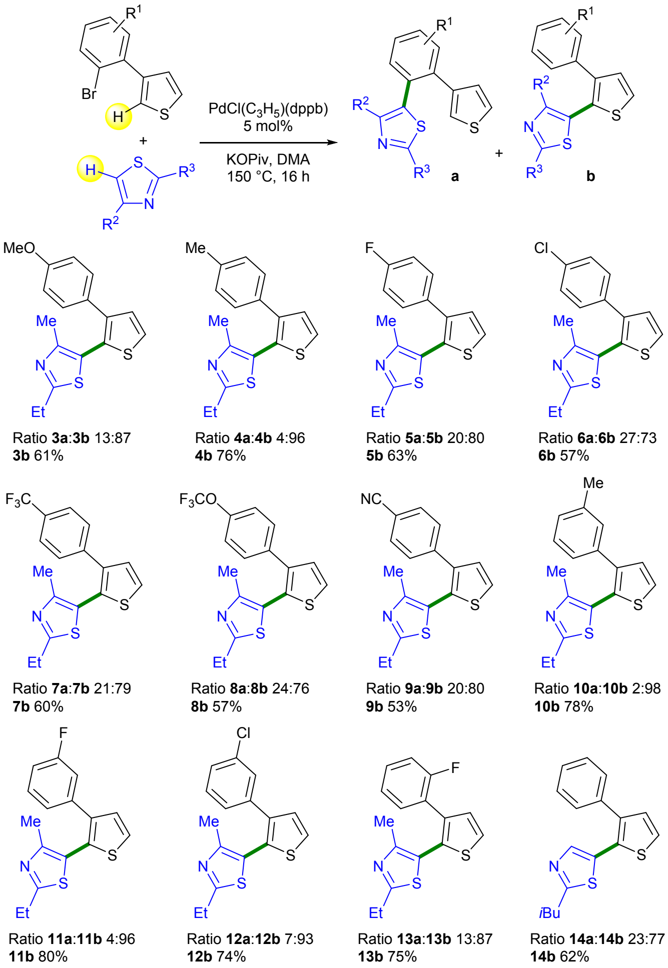
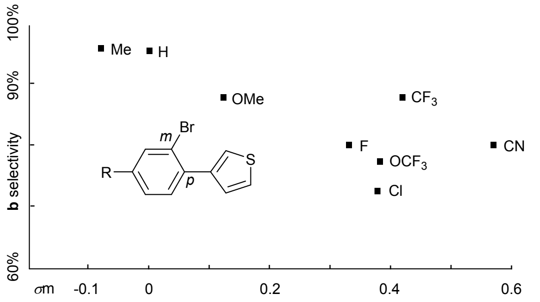
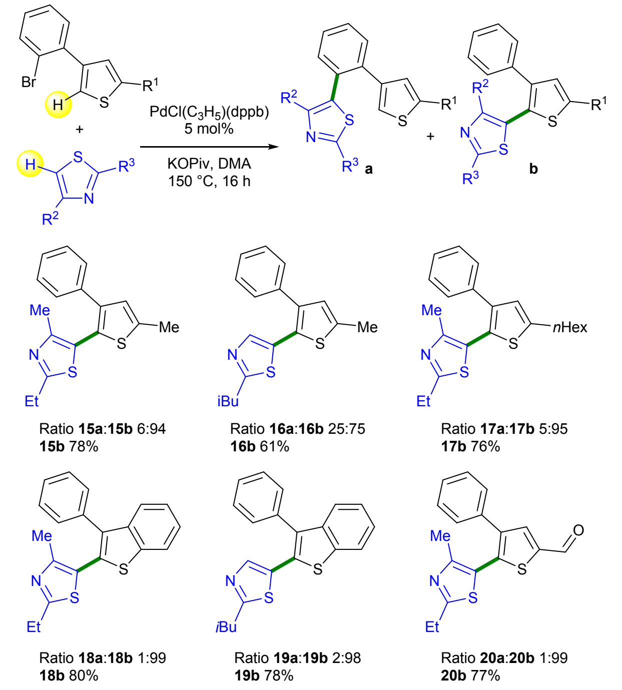


Scheme 3. Pd-catalyzed direct C2-heteroarylations of the thienyl ring of a set of 3-(2-bromoaryl)thiophenes.



Scheme 4. Influence of the substituents on the aryl group of the 3-(2-bromoaryl)thiophenes: correlation of the **a**:**b** selectivity with *meta* Hammett constants.

The impact of the thienyl substituents of 3-(2-bromoaryl)thiophenes on the Pd 1,4-migration process was also examined (Scheme 5). The presence of a methyl substituent at the C5 position of the 3-arylthiophene had almost no effect on the selectivity or yield of the reaction. The desired products, **15b** and **16b**, were obtained with 94% and 75% selectivity, respectively, using 2-ethyl-4-methylthiazole and 2-isobutylthiazole. As expected, the reaction of a 5-hexyl-3-arylthiazole derivative with 2-ethyl-4-methylthiazole produced isomer **17b** with a similar selectivity of 95%. A benzothiophene unit was also well tolerated. In the presence of 3-(2-bromophenyl)benzothiophene **1p**, both 2-ethyl-4-methylthiazole and 2-isobutylthiazole gave the desired products **18b** and **19b** with very high selectivities of 99% and 98%, respectively. The presence of a formyl C2-substituent on the thienyl ring was also tolerated. Using 4-(2-bromophenyl)thiophene-2-carbaldehyde **1o** and 2-ethyl-4-methylthiazole as the coupling partner, the target product **20b** arising from Pd 1,4-migration was also obtained with a very high 99% selectivity and in 77% yield.



Scheme 5. Pd-catalyzed direct C5-heteroarylations of the thienyl ring of 4-(2-bromophenyl)thiophene derivatives.

Then, the heteroarylation of 3-(2-bromophenyl)thiophenes **1j-1m**, using a variety of heteroarenes was explored (Scheme 6). Similar selectivity to that observed with 2-isobutylthiazole was achieved using 2-acetylthiazole, affording product **21b** with 81% selectivity and 68% yield. Regioselectivities of 98% and 94% were obtained for isomers **22b** and **23b**, respectively, when 2-hexylthiophene was used with **1j** and **1m** as the reaction partners. With 2-chlorothiophene, the target product **24b** was obtained with a lower selectivity of 68%. Notably, no cleavage of the thienyl C-Cl bond was observed in the course of this reaction, which allowed for subsequent transformations. The product **25b** was obtained in 96% selectivity from 2-methyl-2-(thien-2-yl)-1,3-dioxolane and 4-(2-bromophenyl)-2-methylthiophene **1m**. Using 2-butylfuran, products **26b** and **27b** were obtained with selectivities of 97%, but in quite low yield due to the formation of unidentified side products. Very high selectivity in isomer **29b** was obtained when 1-methylpyrrole was used; however, unidentified side products were formed again. In the presence of **1l** and **1m**, imidazo[1,2-*a*]pyrazine afforded the target Pd 1,4-migration products **30b**

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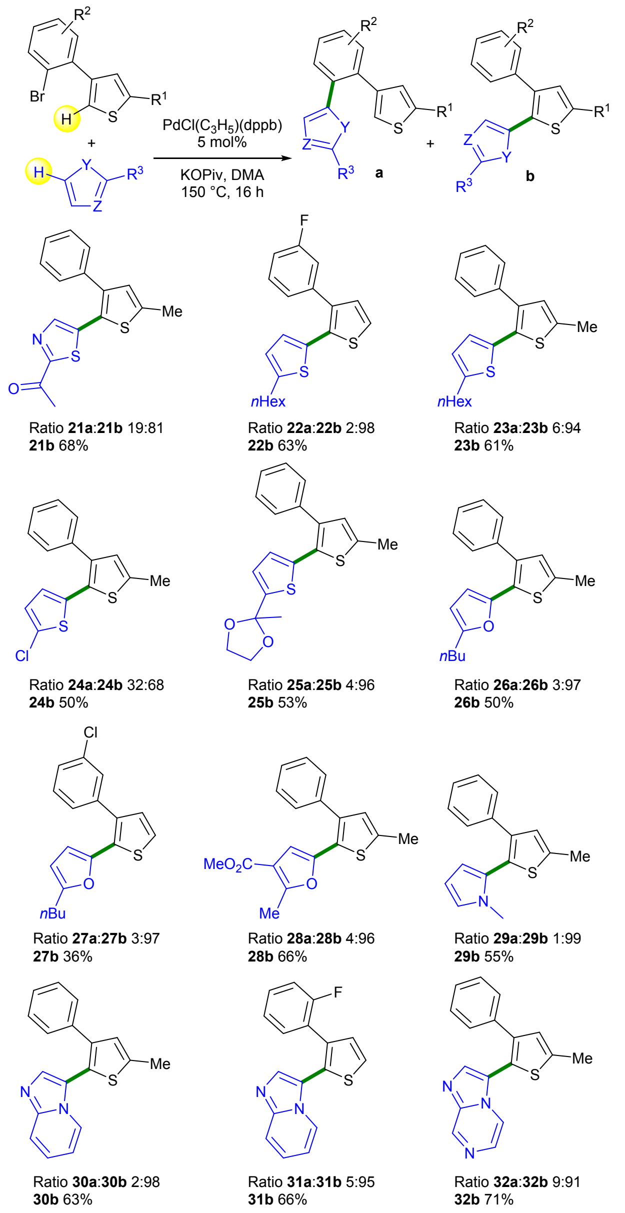
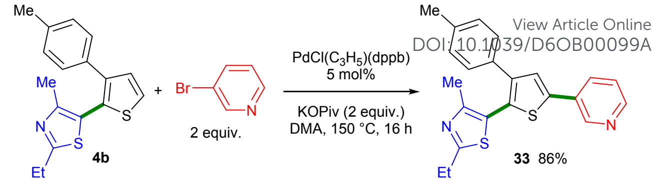
and **31b** with 98% and 95% selectivity, respectively. Finally, a selectivity of 91% in product **32b** was obtained using imidazo[1,2-*a*]pyrazine.



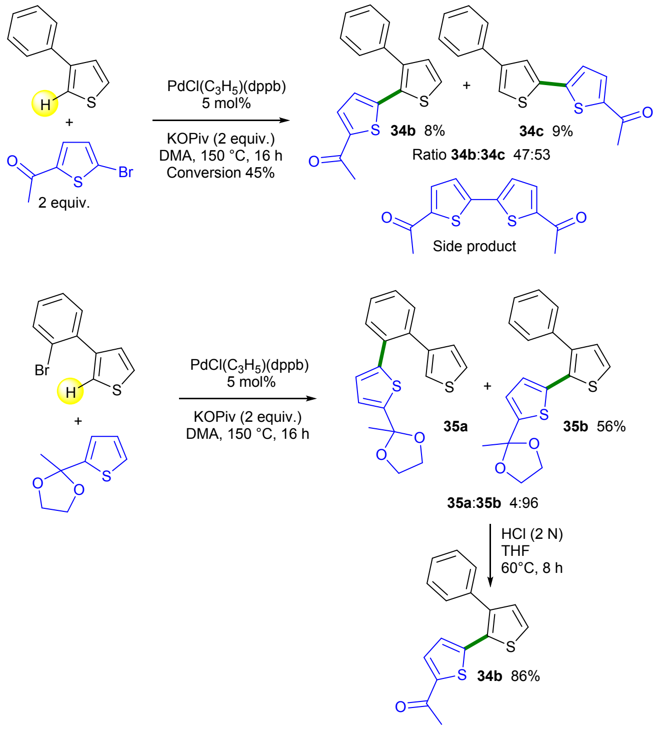
Scheme 6. Pd-catalyzed direct C2- or C5-heteroarylations of the thienyl ring of 3-(2-bromoaryl)thiophenes **1j-1m** using a set of heteroarenes.

The synthesis of a 2,5-diheteroaryl-3-arylthiophene from the 5-(thien-2-yl)thiazole derivative **4b**, prepared in Scheme 3, via Pd-catalyzed direct arylation, was also investigated (Scheme 7). We obtained the desired 2-heteroaryl-3,5-diarylthiophene derivative **33** in an 86% yield from **4b**, 3-bromopyridine, 5 mol% $PdCl(C_3H_5)$(dppb) catalyst, and KOPiv base. This result demonstrates that our method allows for the introduction of two different heteroaryl substituents at positions C2 and C5 of the thienyl unit.



Scheme 7. Preparation of a tri(hetero)arylated thiophene derivative *via* successive Pd-catalyzed direct (hetero)arylations.

To further illustrate the advantage of our method for synthesizing 2-heteroaryl-3-arylthiophenes, we tried to synthesize one of them using palladium-catalyzed coupling of 3-phenylthiophene and a 2-bromothiophene (Scheme 8). We found that preparing 2-thienyl-substituted 3-phenylthiophene **34b** from 3-phenylthiophene and 1-(5-bromothien-2-yl)ethan-1-one was very challenging. A low conversion of 3-phenylthiophene was observed in this reaction. Moreover, we obtained a mixture between the C2 and C5 arylated 3-phenylthiophene in a 47:53 ratio, affording the desired isomer **34b** in only 8% isolated yield (Scheme 8, top). In addition, it should be noted that the formation of a large amount of the side product 1,1'-([2,2'-bithiophene]-5,5'-diyl)bis(ethan-1-one) was also observed. In contrast, our method produced **35b** in 96% selectivity and 56% yield from 3-(2-bromophenyl)thiophene **1a** and 2-methyl-2-(thien-2-yl)-1,3-dioxolane (Scheme 8, bottom). Product **35b** could be easily deprotected under acidic conditions into product **34b** in 86% yield.



Scheme 8. Use of 3-phenylthiophene vs 3-(2-bromophenyl)thiophene **1a** in Pd-catalyzed direct C2-heteroarylation.

Mechanism for the access to **b** products likely proceed *via* a Pd-1,4-migration[29-31] followed by a direct arylation[41-44] as described

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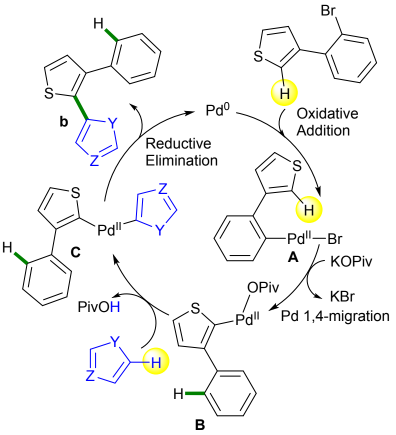
in the Scheme 9. The first step of the catalytic cycle certainly involves the oxidative addition of the 3-(2-bromoaryl)thiophene to palladium to give the intermediate **A**. Then, a Br/OPiv ligand exchange and a Pd-1,4-migration[29-31] occurs to give the intermediate **B**. From **B**, a concerted metallation deprotonation (CMD)[41-44] of the heteroarene coupling partner, gives the intermediate **C**. Finally, reductive elimination regenerates a Pd(0) species and produces the C2-heteroarylated 3-arylthiophene derivative **b**. In the absence of computational studies, we assume that the reaction is driven by the irreversible formation of the C–C bond.



Scheme 9. Proposed catalytic cycle for accessing **b** products.

Conclusions

In summary, Pd 1,4-migration associated with Pd-catalyzed direct arylation allowed for the synthesis of a variety of C2-heteroarylated 3-arylthiophenes in only two steps from commercially available compounds. This method enables the regioselective C2-heteroarylation of the thienyl ring, as the bromo substituent on the 3-arylthiophene behaves as a traceless directing group; whereas the thienyl C5-position remained untouched. This coupling reaction creates a C-C bond between two heteroarenes through the functionalization of two C-H bonds. This reaction is compatible with a variety of heteroarenes, as well as several substituents on the aryl unit of 3-(2-bromoaryl)thiophene. Furthermore, these reactions use an air-stable palladium catalyst associated with an inexpensive base. Therefore, this method is undoubtedly one of the most efficient synthetic pathways for producing C2-heteroarylated 3-arylthiophenes.

Experimental

General

$[PdCl(C_3H_5)]_2$ (98%) was purchased from Aldrich. DMA (99+%) extra pure was purchased from ACROS. Dppb (1,4-bis(diphenylphosphino)butane) (98%), KOPiv (95+%), thien-3-ylboronic acids, 1,2-dihalobenzenes and 3-phenylthiophene were purchased from Fluorochem. These compounds were not purified before use. All reagents were weighed and handled in air. All reactions were carried out under an inert atmosphere with standard Schlenk techniques. ^1H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. High-resolution mass spectra were measured on a Thermo Fisher Scientific Q-Exactive spectrometer. Melting points were determined with a Kofler hot bench system. 3-(2-Bromophenyl)thiophene[35] **1a** and 4-(2-bromophenyl)-2-methylthiophene[36] **1m** were prepared using reported procedures.

Preparation of the PdCl(C_3H_5)(dppb) catalyst:[37]

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.3 (s).

General procedure for the preparation of 3-(2-bromophenyl)thiophenes 1b-1l, 1o and 1p:

As a typical experiment, a mixture of 1,2-dihalobenzene derivative (3 mmol), thien-3-ylboronic acid derivative (4.5 mmol), K_2CO_3 (0.828 g, 6 mmol), $Pd(OAc)_2$ (33.6 mg, 0.15 mmol) and dppf (166.2 mg, 0.30 mmol) in DMA (20 mL) was stirred at 150 °C for 16 h. After being allowed to cool to room temperature, the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the 3-(2-bromoaryl)thiophenes.

3-(2-Bromo-4-methoxyphenyl)thiophene (1b)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-1-iodo-4-methoxybenzene (0.939 g, 3 mmol), **1b** was isolated in 82% (0.661 g) yield as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 6.93 (dd, J = 8.6, 2.6 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 140.9, 131.7, 130.0, 129.1, 124.7, 123.5, 122.9, 118.5, 113.6, 55.6.

HRMS calcd for $[M+H]^+$ $C_{11}H_{10}BrOS$ 268.9630, found: 268.9630.

3-(2-Bromo-4-methylphenyl)thiophene (1c)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-1-iodo-4-methylbenzene (0.891 g, 3 mmol), **1c** was isolated in 84% (0.638 g) yield as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.41 (dd, J = 3.1, 1.3 Hz, 1H), 7.38 (dd, J = 4.9, 3.0 Hz, 1H), 7.35-7.27 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 138.9, 134.6, 133.8, 131.0, 129.0, 128.2, 124.7, 123.7, 122.3, 20.7.

HRMS calcd for $[M+H]^+$ $C_{11}H_{10}BrS$ 252.9681, found: 252.9681.

3-(2-Bromo-4-fluorophenyl)thiophene (1d)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-4-fluoro-1-iodobenzene (0.903 g, 3 mmol), **1d** was isolated in 79% (0.609 g) yield as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.3, 2.6 Hz, 1H), 7.42-7.38 (m, 3H), 7.28 (dd, J = 3.5, 3.0 Hz, 1H), 7.09 (ddd, J = 8.5, 7.9, 2.7 Hz, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2.

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (d, J = 250.8 Hz), 140.1, 133.8 (d, J = 3.7 Hz), 132.1 (d, J = 8.4 Hz), 128.9, 125.0, 124.1, 122.7 (d, J = 9.6 Hz), 120.5 (d, J = 24.3 Hz), 114.6 (d, J = 21.0 Hz).

HRMS calcd for $[M+H]^+$ $C_{10}H_7BrFS$ 256.9430, found: 256.9429.

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3-(2-Bromo-4-chlorophenyl)thiophene (1e)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-4-chloro-1-iodobenzene (0.952 g, 3 mmol), **1e** was isolated in 78% (0.641 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (t, *J* = 1.2 Hz, 1H), 7.42 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.35-7.32 (m, 2H), 7.30-7.25 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 140.0, 136.1, 133.7, 132.9, 131.9, 128.7, 127.6, 125.1, 124.3, 122.9.

HRMS calcd for $[M+H]^+$ $C_{10}H_7BrClS$ 272.9135, found: 272.9135.

3-(2-Bromo-4-(trifluoromethyl)phenyl)thiophene (1f)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (1.053 g, 3 mmol), **1f** was isolated in 74% (0.681 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.50 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.44 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.33 (dd, *J* = 5.0, 1.3 Hz, 1H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -62.6.

^{13}C NMR (101 MHz, CDCl$_3$) δ 141.1, 139.8, 131.5, 130.8 (q, *J* = 33.2 Hz), 130.4 (q, *J* = 3.9 Hz), 128.5, 125.4, 124.9, 124.2 (q, *J* = 3.6 Hz), 122.7, 120.3 (d, *J* = 272.5 Hz).

HRMS calcd for $[M]^+$ $C_{11}H_6BrF_3S$ 305.9320, found: 305.9322.

3-(2-Bromo-4-(trifluoromethoxy)phenyl)thiophene (1g)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 2-bromo-1-iodo-4-(trifluoromethoxy)benzene (1.101 g, 3 mmol), **1g** was isolated in 84% (0.814 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 s, 1H), 7.49-7.40 (m, 3H), 7.32 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -57.9.

^{13}C NMR (101 MHz, CDCl$_3$) δ 148.3 (q, *J* = 2.0 Hz), 139.8, 136.5, 131.9, 128.7, 125.9, 125.2, 124.5, 122.9, 120.4 (d, *J* = 258.4 Hz), 119.9.

HRMS calcd for $[M]^+$ $C_{11}H_6BrF_3OS$ 321.9269, found: 321.9271.

3-Bromo-4-(thien-3-yl)benzonitrile (1h)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 3-bromo-4-iodobenzonitrile (0.924 g, 3 mmol), **1h** was isolated in 73% (0.576 g) yield as a white solid: mp 76-78 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, *J* = 1.7 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.53 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.32 (dd, *J* = 5.0, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 142.2, 139.3, 136.7, 131.7, 130.9, 128.4, 125.8, 125.6, 122.8, 117.4, 112.4.

HRMS calcd for $[M+H]^+$ $C_{11}H_7BrNS$ 263.9477, found: 263.9477.

3-(2-Bromo-5-methylphenyl)thiophene (1i)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 1-bromo-2-iodo-4-methylbenzene (0.891 g, 3 mmol), **1i** was isolated in 76% (0.577 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.40 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.33 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.26 (s, 1H), 7.04 (ddd, *J* = 8.1, 2.2, 0.8 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 141.3, 137.3, 137.2, 133.1, 132.1, 129.6, 129.0, 124.7, 123.9, 119.2, 20.9.

HRMS calcd for $[M+H]^+$ $C_{11}H_{10}BrS$ 252.9681, found: 252.9681.

3-(2-Bromo-5-fluorophenyl)thiophene (1j)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 1-bromo-4-fluoro-2-iodobenzene (0.903 g, 3 mmol), **1j** was isolated in 81% (0.624 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.47 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.41 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.31 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.15 (dd, *J* = 9.3, 3.1 Hz, 1H), 6.94 (ddd, *J* = 8.8, 7.8, 3.1 Hz, 1H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -115.1.

^{13}C NMR (101 MHz, CDCl$_3$) δ 161.8 (d, *J* = 247.3 Hz), 140.1 (d, *J* = 1.5 Hz), 139.2 (d, *J* = 8.1 Hz), 134.6 (d, *J* = 8.1 Hz), 128.6, 125.2, 124.6, 118.2 (d, *J* = 23.0 Hz), 116.7 (d, *J* = 3.2 Hz), 115.8 (d, *J* = 22.3 Hz).

HRMS calcd for $[M]^+$ $C_{10}H_6BrFS$ 255.9352, found: 255.9353.

3-(2-Bromo-5-chlorophenyl)thiophene (1k)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 1-bromo-4-chloro-2-iodobenzene (0.952 g, 3 mmol), **1k** was isolated in 80% (0.656 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, *J* = 8.5 Hz, 1H), 7.46 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.43-7.37 (m, 2H), 7.30 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 139.9, 139.0, 134.4, 133.3, 131.1, 128.7, 128.6, 125.2, 124.6, 120.5.

HRMS calcd for $[M+H]^+$ $C_{10}H_7BrClS$ 272.9135, found: 272.9135.

3-(2-Bromo-6-fluorophenyl)thiophene (1l)

From thien-3-ylboronic acid (0.572 g, 4.5 mmol) and 1-bromo-3-fluoro-2-iodobenzene (0.903 g, 3 mmol), **1l** was isolated in 83% (0.640 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.48-7.42 (m, 2H), 7.27-7.11 (m, 3H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -109.0.

^{13}C NMR (101 MHz, CDCl$_3$) δ 160.4 (d, *J* = 249.9 Hz), 133.4, 129.6 (d, *J* = 9.1 Hz), 129.2 (d, *J* = 1.5 Hz), 128.8 (d, *J* = 3.5 Hz), 126.3 (d, *J* = 18.1 Hz), 125.9 (d, *J* = 1.9 Hz), 124.8, 124.5 (d, *J* = 2.8 Hz), 114.9 (d, *J* = 23.5 Hz).

HRMS calcd for $[M+H]^+$ $C_{10}H_7BrFS$ 256.9430, found: 256.9429.

4-(2-Bromophenyl)-2-hexylthiophene (1n)

Following the procedure of ref 36, from 2-hexylthiophene (0.756 g, 4.5 mmol) and 2-bromobenzenesulfonyl chloride (0.765 g, 3 mmol), **1n** was isolated in 71% (0.688 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.34 (td, *J* = 7.5, 1.3 Hz, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.17 (td, *J* = 7.5, 1.7 Hz, 1H), 6.99 (s, 1H), 2.87 (t, *J* = 7.6 Hz, 2H), 1.75 (quint., *J* = 7.6 Hz, 2H), 1.50-1.21 (m, 6H), 0.95 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 145.2, 140.6, 138.0, 133.3, 131.2, 128.5, 127.3, 125.9, 122.5, 121.5, 31.6, 30.1, 28.8, 22.6, 14.1.

HRMS calcd for $[M+H]^+$ $C_{16}H_{20}BrS$ 323.0464, found: 323.0464.

4-(2-Bromophenyl)thiophene-2-carbaldehyde (1o)

From (5-formylthien-3-yl)boronic acid (0.702 g, 4.5 mmol) and 1-bromo-2-iodobenzene (0.849 g, 3 mmol), **1o** was isolated in 69% (0.552 g) yield as a colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 10.00 (d, *J* = 1.3 Hz, 1H), 7.97 (d, *J* = 1.5 Hz, 1H), 7.83 (t, *J* = 1.4 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.47-7.36 (m, 2H), 7.30-7.22 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 182.9, 143.4, 142.3, 137.5, 135.9, 133.5, 133.4, 131.0, 129.5, 127.7, 122.4.

HRMS calcd for $[M+H]^+$ $C_{11}H_8BrOS$ 266.9474, found: 266.9474.

3-(2-Bromophenyl)benzo[*b*]thiophene (1p)[45]

From benzo[*b*]thien-3-ylboronic acid (0.801 g, 4.5 mmol) and 1-bromo-2-iodobenzene (0.849 g, 3 mmol), **1p** was isolated in 85% (0.737 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.68-7.59 (m, 1H), 7.55-7.42 (m, 5H), 7.36 (ddd, *J* = 8.0, 6.5, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 139.9, 138.5, 136.9, 136.7, 133.3, 132.1, 129.5, 127.4, 125.5, 124.6, 124.4, 124.2, 123.4, 122.9.
LRMS calcd for [M]$^+$ $C_{14}H_9BrS$ 290, found: 290.

General procedure for the preparation of products 2b-35b:
As a typical experiment, the reaction of the 3-(2-bromoaryl)thiophene derivative **1a**-**1p** (1 mmol), heteroarene (2 mmol) and KOPiv (0.280 g, 2 mmol) at 150 °C during 16 h in DMA (4 mL) in the presence of PdCl(C_3H_5)(dppb) (30.5 mg, 0.05 mmol) under argon affords the coupling product after evaporation of the solvent and purification by column chromatography on silica gel. The **a**:**b** ratios were determined by ^{1}H NMR and GC/MS analysis of the crude mixtures.

2-Ethyl-4-methyl-5-(3-phenylthien-2-yl)thiazole (2b)
From 3-(2-bromophenyl)thiophene **1a** (0.239 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **2a** and **2b** was obtained in 5:95 ratio and **2b** was isolated in 77% (0.219 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, *J* = 5.3 Hz, 1H), 7.37-7.25 (m, 5H), 7.23 (d, *J* = 5.3 Hz, 1H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.08 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.1, 150.1, 141.4, 136.0, 129.5, 128.5, 128.4, 127.5, 127.1, 126.1, 122.7, 27.0, 15.7, 14.1.
HRMS calcd for [M+H]$^+$ $C_{16}H_{16}NS_2$ 286.0719, found: 286.0717.

2-Ethyl-4-methyl-5-(2-(thien-3-yl)phenyl)thiazole (2a)
From 3-(2-bromophenyl)thiophene **1a** (0.239 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), using Cs_2CO_3 (0.652, 2 mmol) as the base, a mixture of **2a** and **2b** was obtained in 65:35 ratio and **2a** was isolated in 41% (0.117 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.47-7.34 (m, 3H), 7.21 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.10 (dd, *J* = 2.9, 1.3 Hz, 1H), 6.86 (dd, *J* = 5.0, 1.3 Hz, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 171.2, 148.3, 141.3, 137.2, 132.1, 130.3, 129.9, 129.7, 128.6, 128.2, 127.2, 125.0, 123.0, 26.9, 15.3, 14.3.
HRMS calcd for [M+H]$^+$ $C_{16}H_{16}NS_2$ 286.0719, found: 286.0719.

2-Ethyl-5-(3-(4-methoxyphenyl)thien-2-yl)-4-methylthiazole (3b)
From 3-(2-bromo-4-methoxyphenyl)thiophene **1b** (0.268 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **3a** and **3b** was obtained in 13:87 ratio and **3b** was isolated in 61% (0.192 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 5.3 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.11 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.0, 158.7, 150.1, 141.0, 129.5, 129.4, 128.5, 126.5, 126.0, 122.9, 114.0, 55.2, 27.0, 15.7, 14.1.
HRMS calcd for [M+H]$^+$ $C_{17}H_{18}NOS_2$ 316.0824, found: 316.0825.

2-Ethyl-4-methyl-5-(3-(*p*-tolyl)thien-2-yl)thiazole (4b)
From 3-(2-bromo-4-methylphenyl)thiophene **1c** (0.253 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **4a** and **4b** was obtained in 4:96 ratio and **4b** was isolated in 76% (0.227 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, *J* = 5.3 Hz, 1H), 7.27-7.16 (m, 3H), 7.12 (d, *J* = 8.4 Hz, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 2.09 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.0, 150.1, 141.4, 136.9, 133.0, 129.5, 129.2, 128.2, 127.0, 126.0, 122.8, 27.0, 21.2, 15.7, 14.1.
HRMS calcd for [M+H]$^+$ $C_{17}H_{18}NS_2$ 300.0875, found: 300.0873.

2-Ethyl-5-(3-(4-fluorophenyl)thien-2-yl)-4-methylthiazole (5b)
From 3-(2-bromo-4-fluorophenyl)thiophene **1d** (0.257 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **5a** and **5b** was obtained in 20:80 ratio and **5b** was isolated in 63% (0.191 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, *J* = 5.3 Hz, 1H), 7.26 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.19 (d, *J* = 5.3 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).
^{19}F NMR (376 MHz, CDCl$_3$) δ -114.8.
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.3, 162.0 (d, *J* = 246.9 Hz), 150.2, 140.3, 132.0 (d, *J* = 3.4 Hz), 130.0 (d, *J* = 8.1 Hz), 129.3, 127.5, 126.3, 122.4, 115.5 (d, *J* = 21.4 Hz), 27.0, 15.7, 14.1.
HRMS calcd for [M+H]$^+$ $C_{16}H_{15}FNS_2$ 304.0625, found: 304.0624.

5-(3-(4-Chlorophenyl)thien-2-yl)-2-ethyl-4-methylthiazole (6b)
From 3-(2-bromo-4-chlorophenyl)thiophene **1e** (0.274 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **6a** and **6b** was obtained in 27:73 ratio and **6b** was isolated in 57% (0.182 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 5.2 Hz, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.4, 150.3, 140.1, 134.4, 133.1, 129.7, 129.1, 128.8, 127.9, 126.5, 122.3, 27.0, 15.7, 14.0.
HRMS calcd for [M+H]$^+$ $C_{16}H_{15}ClNS_2$ 320.0329, found: 320.0329.

2-Ethyl-4-methyl-5-(3-(4-(trifluoromethyl)phenyl)thien-2-yl)thiazole (7b)
From 3-(2-bromo-4-(trifluoromethyl)phenyl)thiophene **1f** (0.307 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **7a** and **7b** was obtained in 21:79 ratio and **7b** was isolated in 60% (0.212 g) yield as a yellow solid: mp 116-118 °C.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 5.3 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 5.3 Hz, 1H), 3.00 (q, *J* = 7.6 Hz, 2H), 2.08 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).
^{19}F NMR (376 MHz, CDCl$_3$) δ -62.6.
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.6, 150.4, 139.8, 139.5, 129.2 (q, *J* = 32.6 Hz), 129.1, 128.9, 128.6, 126.7, 125.5 (q, *J* = 3.9 Hz), 122.0, 121.2 (q, *J* = 272.0 Hz), 27.0, 15.7, 14.0.
HRMS calcd for [M+H]$^+$ $C_{17}H_{15}F_3NS_2$ 354.0593, found: 354.0591.

2-Ethyl-4-methyl-5-(3-(4-(trifluoromethoxy)phenyl)thien-2-yl)thiazole (8b)
From 3-(2-bromo-4-(trifluoromethoxy)phenyl)thiophene **1g** (0.323 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **8a** and **8b** was obtained in 24:76 ratio and **8b** was isolated in 57% (0.210 g) yield as a yellow oil.
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, *J* = 5.2 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 5.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.09 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).
^{19}F NMR (376 MHz, CDCl$_3$) δ -57.8.
^{13}C NMR (101 MHz, CDCl$_3$) δ 172.4, 150.3, 148.3 (q, *J* = 1.8 Hz), 139.8, 134.6, 129.7, 129.2, 128.1, 126.5, 122.2, 120.9, 120.5 (q, *J* = 257.3 Hz), 27.0, 15.7, 14.0.
HRMS calcd for [M+H]$^+$ $C_{17}H_{15}F_3NOS$ 370.0542, found: 370.0542.

4-(2-(2-Ethyl-4-methylthiazol-5-yl)thien-3-yl)benzonitrile (9b)
From 3-bromo-4-(thien-3-yl)benzonitrile **1h** (0.264 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **9a** and **9b** was

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obtained in 20:80 ratio and **9b** was isolated in 53% (0.164 g) yield as a white solid: mp 118-120 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 5.3 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 5.3 Hz, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.09 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 150.5, 140.5, 139.3, 132.4, 129.5, 128.9, 128.8, 127.0, 121.7, 118.8, 110.8, 27.0, 15.7, 14.0.

HRMS calcd for $[M+H]^+$ $C_{17}H_{15}N_2S_2$ 311.0671, found: 311.0671.

2-Ethyl-4-methyl-5-(3-(*m*-tolyl)thien-2-yl)thiazole (10b)

From 3-(2-bromo-5-methylphenyl)thiophene **1i** (0.253 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **10a** and **10b** was obtained in 2:98 ratio and **10b** was isolated in 78% (0.233 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 5.2 Hz, 1H), 7.21 (d, *J* = 5.3 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 7.11-7.02 (m, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 2.11 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 150.1, 141.5, 138.0, 135.9, 129.5, 129.1, 128.4, 127.9, 127.3, 126.0, 125.5, 122.7, 27.0, 21.5, 15.8, 14.2.

HRMS calcd for $[M+H]^+$ $C_{17}H_{18}NS_2$ 300.0875, found: 300.0873.

2-Ethyl-5-(3-(3-fluorophenyl)thien-2-yl)-4-methylthiazole (11b)

From 3-(2-bromo-5-fluorophenyl)thiophene **1j** (0.257 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **11a** and **11b** was obtained in 4:96 ratio and **11b** was isolated in 80% (0.242 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.3 Hz, 1H), 7.31-7.24 (m, 1H), 7.20 (d, *J* = 5.3 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.04-6.93 (m, 2H), 2.99 (q, *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.9.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 162.8 (d, *J* = 245.8 Hz), 150.3, 140.0 (d, *J* = 2.3 Hz), 138.1 (d, *J* = 8.1 Hz), 130.0 (d, *J* = 8.5 Hz), 129.2, 128.3, 126.4, 124.1 (d, *J* = 3.0 Hz), 122.1, 115.3 (d, *J* = 22.2 Hz), 114.1 (d, *J* = 21.1 Hz), 27.0, 15.7, 14.1.

HRMS calcd for $[M+H]^+$ $C_{16}H_{15}FNS_2$ 304.0625, found: 304.0625.

5-(3-(3-Chlorophenyl)thien-2-yl)-2-ethyl-4-methylthiazole (12b)

From 3-(2-bromo-5-chlorophenyl)thiophene **1k** (0.274 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **12a** and **12b** was obtained in 7:93 ratio and **12b** was isolated in 74% (0.237 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.2 Hz, 1H), 7.31 (s, 1H), 7.30-7.22 (m, 2H), 7.20 (d, *J* = 5.3 Hz, 1H), 7.14 (dt, *J* = 6.7, 1.8 Hz, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 150.4, 139.8, 137.7, 134.3, 129.7, 129.1, 128.4, 128.4, 127.3, 126.6, 126.5, 122.1, 27.0, 15.8, 14.1.

HRMS calcd for $[M+H]^+$ $C_{16}H_{15}ClNS_2$ 320.0329, found: 320.0330.

2-Ethyl-5-(3-(2-fluorophenyl)thien-2-yl)-4-methylthiazole (13b)

From 3-(2-bromo-6-fluorophenyl)thiophene **1l** (0.257 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **13a** and **13b** was obtained in 13:87 ratio and **13b** was isolated in 75% (0.227 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 5.3 Hz, 1H), 7.34-7.25 (m, 1H), 7.21 (dd, *J* = 5.3, 2.0 Hz, 1H), 7.16 (td, *J* = 7.5, 1.9 Hz, 1H), 7.13-7.03 (m, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.36 (t, *J* = 7.6 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 159.8 (d, *J* = 248.1 Hz), 150.0, 135.1, 131.4 (d, *J* = 3.4 Hz), 130.1 (d, *J* = 2.7 Hz), 129.9, 129.3 (d, *J* = 8.2 Hz), 125.8, 124.1 (d, *J* = 3.7 Hz), 123.8 (d, *J* = 15.0 Hz), 122.3, 116.0 (d, *J* = 22.3 Hz), 27.0, 15.7, 14.0.

HRMS calcd for $[M+H]^+$ $C_{16}H_{15}FNS_2$ 304.0625, found: 304.0625.

2-Isobutyl-5-(3-phenylthien-2-yl)thiazole (14b)

From 3-(2-bromophenyl)thiophene **1a** (0.239 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), a mixture of **14a** and **14b** was obtained in 23:77 ratio and **14b** was isolated in 62% (0.185 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.40-7.34 (m, 5H), 7.33 (d, *J* = 5.2 Hz, 1H), 7.12 (d, *J* = 5.3 Hz, 1H), 2.79 (d, *J* = 7.1 Hz, 2H), 2.15-1.93 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 140.7, 140.3, 135.8, 130.4, 130.1, 129.2, 128.5, 127.9, 127.7, 124.7, 42.3, 29.7, 22.2.

HRMS calcd for $[M+H]^+$ $C_{17}H_{18}NS_2$ 300.0875, found: 300.0873.

2-Ethyl-4-methyl-5-(5-methyl-3-phenylthien-2-yl)thiazole (15b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **15a** and **15b** was obtained in 6:94 ratio and **15b** was isolated in 78% (0.233 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 6H), 2.97 (q, *J* = 7.6 Hz, 2H), 2.54 (d, *J* = 1.1 Hz, 3H), 2.07 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 149.8, 141.3, 140.5, 136.2, 128.4, 128.3, 127.7, 127.0, 124.8, 123.1, 27.0, 15.7, 15.3, 14.1.

HRMS calcd for $[M+H]^+$ $C_{17}H_{18}NS_2$ 300.0875, found: 300.0875.

2-Isobutyl-5-(5-methyl-3-phenylthien-2-yl)thiazole (16b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), a mixture of **16a** and **16b** was obtained in 25:75 ratio and **16b** was isolated in 61% (0.191 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.37-7.28 (m, 5H), 6.79 (q, *J* = 1.1 Hz, 1H), 2.77 (d, *J* = 7.2 Hz, 2H), 2.52 (d, *J* = 1.1 Hz, 3H), 2.15-1.93 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 140.2, 139.2, 136.1, 130.4, 129.1, 128.8, 128.4, 127.5, 125.3, 42.3, 29.7, 22.2, 15.2.

HRMS calcd for $[M+H]^+$ $C_{18}H_{20}NS_2$ 314.1032, found: 314.1031.

2-Ethyl-5-(5-hexyl-3-phenylthien-2-yl)-4-methylthiazole (17b)

From 4-(2-bromophenyl)-2-hexylthiophene **1n** (0.323 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **17a** and **17b** was obtained in 5:95 ratio and **17b** was isolated in 76% (0.281 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.14 (m, 5H), 6.91 (s, 1H), 2.97 (q, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 3H), 1.88-1.70 (m, 2H), 1.52-1.30 (m, 6H), 1.37 (t, *J* = 7.6 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 149.7, 146.6, 140.9, 136.3, 128.4, 128.3, 126.9, 126.5, 124.5, 123.3, 31.6, 31.4, 30.2, 28.9, 27.0, 22.6, 15.7, 14.1.

HRMS calcd for $[M+H]^+$ $C_{22}H_{28}NS_2$ 370.1658, found: 370.1655.

2-Ethyl-4-methyl-5-(3-phenylbenzo[*b*]thien-2-yl)thiazole (18b)

From 3-(2-bromophenyl)benzo[*b*]thiophene **1p** (0.289 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **18a** and **18b** was obtained in 1:99 ratio and **18b** was isolated in 80% (0.268 g) yield as a white solid: mp 112-114 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.46-7.32 (m, 7H), 2.96 (q, *J* = 7.6 Hz, 2H), 2.15 (s, 3H), 1.37 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 150.5, 139.8, 139.6, 136.8, 134.8, 130.0, 129.2, 128.7, 127.6, 125.1, 124.7, 123.5, 122.7, 122.1, 27.0, 16.1, 14.1.

HRMS calcd for $[M+H]^+$ $C_{20}H_{18}NS_2$ 336.0875, found: 336.0872.

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2-Isobutyl-5-(3-phenylbenzo[*b*]thien-2-yl)thiazole (19b)

From 3-(2-bromophenyl)benzo[*b*]thiophene **1p** (0.289 g, 1 mmol) and 2-isobutylthiazole (0.282 g, 2 mmol), a mixture of **19a** and **19b** was obtained in 2:98 ratio and **19b** was isolated in 78% (0.272 g) yield as a yellow solid: mp 67-69 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.57-7.47 (m, 3H), 7.47-7.27 (m, 5H), 2.77 (d, *J* = 7.2 Hz, 2H), 2.15-1.93 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 170.9, 141.0, 140.9, 138.2, 134.8, 134.7, 130.5, 130.4, 129.5, 129.0, 128.4, 125.2, 124.7, 123.4, 121.9, 42.2, 29.7, 22.2.

HRMS calcd for [M+H]$^+$ C$_{21}$H$_{20}$NS$_2$ 350.1032, found: 350.1028.

5-(2-Ethyl-4-methylthiazol-5-yl)-4-phenylthiophene-2-carbaldehyde (20b)

From 4-(2-bromophenyl)thiophene-2-carbaldehyde **1o** (0.267 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), a mixture of **20a** and **20b** was obtained in 1:99 ratio and **20b** was isolated in 77% (0.241 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.96 (s, 1H), 7.85 (s, 1H), 7.40-7.33 (m, 3H), 7.32-7.26 (m, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 2.13 (s, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.7, 173.2, 151.2, 142.8, 142.3, 137.9, 137.8, 134.7, 128.8, 128.4, 128.0, 121.6, 27.0, 16.1, 14.0.

HRMS calcd for [M+H]$^+$ C$_{17}$H$_{16}$NOS$_2$ 314.0668, found: 314.0666.

1-(5-(5-Methyl-3-phenylthien-2-yl)thiazol-2-yl)ethan-1-one (21b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 1-(thiazol-2-yl)ethan-1-one (0.254 g, 2 mmol), a mixture of **21a** and **21b** was obtained in 19:81 ratio and **21b** was isolated in 68% (0.203 g) yield as a yellow solid: mp 116-118 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (s, 1H), 7.40 (m, 3H), 7.36-7.30 (m, 2H), 6.81 (q, *J* = 1.1 Hz, 1H), 2.65 (s, 3H), 2.55 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 191.6, 164.8, 142.3, 141.9, 141.3, 139.6, 135.6, 129.6, 129.0, 128.9, 128.2, 124.5, 25.7, 15.3.

HRMS calcd for [M+H]$^+$ C$_{16}$H$_{14}$NOS$_2$ 300.0511, found: 300.0510.

3-(3-Fluorophenyl)-5'-hexyl-2,2'-bithiophene (22b)

From 3-(2-bromo-5-fluorophenyl)thiophene **1j** (0.257 g, 1 mmol) and 2-hexylthiophene (0.336 g, 2 mmol), a mixture of **22a** and **22b** was obtained in 2:98 ratio and **22b** was isolated in 63% (0.217 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.30 (m, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.10 (ddd, *J* = 10.0, 2.6, 1.6 Hz, 1H), 7.07 (d, *J* = 5.2 Hz, 1H), 7.02 (tdd, *J* = 8.5, 2.6, 1.0 Hz, 1H), 6.80 (d, *J* = 3.5 Hz, 1H), 6.63 (d, *J* = 3.3 Hz, 1H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.64 (quint., *J* = 7.4 Hz, 2H), 1.42-1.17 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -113.4.

^{13}C NMR (101 MHz, CDCl$_3$) δ 162.7 (d, *J* = 245.6 Hz), 147.1, 138.6 (d, *J* = 8.1 Hz), 137.0 (d, *J* = 2.2 Hz), 132.9, 132.6, 130.1, 129.7 (d, *J* = 8.4 Hz), 126.7, 125.0 (d, *J* = 3.0 Hz), 124.3, 123.9, 116.2 (d, *J* = 21.9 Hz), 114.1 (d, *J* = 21.0 Hz), 31.5, 31.5, 30.1, 28.7, 22.6, 14.0.

HRMS calcd for [M+H]$^+$ C$_{20}$H$_{22}$FS$_2$ 345.1142, found: 345.1143.

5'-Hexyl-5-methyl-3-phenyl-2,2'-bithiophene (23b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-hexylthiophene (0.336 g, 2 mmol), a mixture of **23a** and **23b** was obtained in 6:94 ratio and **23b** was isolated in 61% (0.207 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 – 7.27 (m, 5H), 6.76 (d, *J* = 1.2 Hz, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.51 (d, *J* = 1.2 Hz, 3H), 1.64 (quint., *J* = 7.4 Hz, 2H), 1.41-1.30 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 146.1, 138.2, 137.9, 136.7, 133.6, 129.7, 129.2, 128.8, 128.2, 127.1, 125.8, 124.0, 31.5, 31.4, 30.1, 28.7, 22.6, 15.2, 14.0.

HRMS calcd for [M+H]$^+$ C$_{21}$H$_{25}$S$_2$ 341.1392, found: 341.1389.

5'-Chloro-5-methyl-3-phenyl-2,2'-bithiophene (24b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-chlorothiophene (0.237 g, 2 mmol), a mixture of **24a** and **24b** was obtained in 32:68 ratio and **24b** was isolated in 50% (0.145 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.33 (m, 5H), 6.76 (q, *J* = 1.1 Hz, 1H), 6.74 (d, *J* = 3.9 Hz, 1H), 6.72 (d, *J* = 3.9 Hz, 1H), 2.51 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 139.3, 138.9, 136.1, 135.1, 129.4, 129.2, 128.9, 128.5, 128.2, 127.5, 126.1, 125.2, 15.2.

HRMS calcd for [M+H]$^+$ C$_{16}$H$_{12}$ClS$_2$ 291.0064, found: 291.0064.

2-Methyl-2-(5'-methyl-3'-phenyl-[2,2'-bithiophen]-5-yl)-1,3-dioxolane (25b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-methyl-2-(thien-2-yl)-1,3-dioxolane (0.340 g, 2 mmol), a mixture of **25a** and **25b** was obtained in 4:96 ratio and **25b** was isolated in 53% (0.181 g) yield as a colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43-7.30 (m, 5H), 6.84 (d, *J* = 3.6 Hz, 1H), 6.76 (q, *J* = 1.1 Hz, 1H), 6.73 (d, *J* = 3.7 Hz, 1H), 4.17-3.93 (m, 4H), 2.51 (d, *J* = 1.1 Hz, 3H), 1.75 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 146.8, 138.8, 138.4, 136.5, 136.0, 129.1, 129.0, 128.9, 128.3, 127.2, 125.7, 124.2, 107.1, 64.9, 27.3, 15.2.

HRMS calcd for [M+H]$^+$ C$_{19}$H$_{19}$O$_2$S$_2$ 343.0821, found: 343.0822.

2-Butyl-5-(5-methyl-3-phenylthien-2-yl)furan (26b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 2-butylfuran (0.248 g, 2 mmol), a mixture of **26a** and **26b** was obtained in 3:97 ratio and **26b** was isolated in 50% (0.148 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45-7.24 (m, 5H), 6.73 (q, *J* = 1.1 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 5.90 (d, *J* = 3.2 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.52 (d, *J* = 1.1 Hz, 3H), 1.65-1.52 (m, 2H), 1.44-1.27 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 155.6, 146.9, 137.8, 137.4, 137.1, 128.9, 128.7, 128.2, 127.1, 126.4, 107.2, 106.5, 30.2, 27.7, 22.2, 15.2, 13.8.

HRMS calcd for [M+H]$^+$ C$_{19}$H$_{21}$OS 297.1308, found: 297.1306.

2-Butyl-5-(3-(3-chlorophenyl)thien-2-yl)furan (27b)

From 3-(2-bromo-5-chlorophenyl)thiophene **1k** (0.274 g, 1 mmol) and 2-butylfuran (0.248 g, 2 mmol), a mixture of **27a** and **27b** was obtained in 3:97 ratio and **27b** was isolated in 36% (0.114 g) yield as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (s, 1H), 7.33-7.29 (m, 3H), 7.26 (d, *J* = 5.1 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 5.95 (d, *J* = 3.3 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.67-1.51 (m, 2H), 1.46-1.30 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 156.4, 146.3, 138.7, 135.9, 134.1, 130.1, 129.6, 129.5, 129.1, 127.3, 127.2, 123.7, 108.2, 106.7, 30.2, 27.7, 22.2, 13.8.

HRMS calcd for [M+H]$^+$ C$_{18}$H$_{18}$ClOS 317.0761, found: 317.0761.

Methyl 2-methyl-5-(5-methyl-3-phenylthien-2-yl)furan-3-carboxylate (28b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and methyl 2-methylfuran-3-carboxylate (0.280 g, 2 mmol), a

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mixture of **28a** and **28b** was obtained in 4:96 ratio and **28b** was isolated in 66% (0.206 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65-7.31 (m, 5H), 6.75 (q, *J* = 1.2 Hz, 1H), 6.29 (s, 1H), 3.79 (s, 3H), 2.56 (s, 3H), 2.53 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 164.3, 158.1, 146.7, 139.0, 139.0, 136.5, 128.9, 128.7, 128.4, 127.5, 124.6, 114.8, 106.9, 51.3, 15.2, 13.7.

HRMS calcd for [M+H]$^+$ $C_{18}H_{17}O_3S$ 313.0893, found: 313.0892.

1-Methyl-2-(5-methyl-3-phenylthien-2-yl)pyrrole (29b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and 1-methylpyrrole (0.243 g, 3 mmol), a mixture of **29a** and **29b** was obtained in 1:99 ratio and **29b** was isolated in 55% (0.139 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31-7.24 (m, 3H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.97 (q, *J* = 1.2 Hz, 1H), 6.74-6.54 (m, 1H), 6.27 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.19 (dd, *J* = 3.6, 2.7 Hz, 1H), 3.08 (s, 3H), 2.54 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 139.5, 139.4, 136.8, 128.5, 127.7, 127.1, 126.7, 126.6, 125.7, 122.9, 111.1, 107.8, 34.0, 15.3.

HRMS calcd for [M+H]$^+$ $C_{16}H_{16}NS$ 254.0998, found: 254.0995.

3-(5-Methyl-3-phenylthien-2-yl)imidazo[1,2-*a*]pyridine (30b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.236 g, 2 mmol), a mixture of **30a** and **30b** was obtained in 2:98 ratio and **30b** was isolated in 63% (0.183 g) yield as a white solid: mp 120-122 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.59 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.21-7.15 (m, 5H), 7.12 (dd, *J* = 9.1, 6.9 Hz, 1H), 7.07 (q, *J* = 1.1 Hz, 1H), 6.55 (t, *J* = 6.8 Hz, 1H), 2.59 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 146.0, 141.5, 140.8, 135.9, 134.8, 128.7, 127.9, 127.3, 127.2, 124.5, 124.2, 121.1, 118.2, 117.7, 112.1, 15.4.

HRMS calcd for [M+H]$^+$ $C_{18}H_{15}N_2S$ 291.0550, found: 291.0548.

3-(3-(2-Fluorophenyl)thien-2-yl)imidazo[1,2-*a*]pyridine (31b)

From 3-(2-bromo-6-fluorophenyl)thiophene **1l** (0.257 g, 1 mmol) imidazo[1,2-*a*]pyrazine (0.238 g, 2 mmol), a mixture of **31a** and **31b** was obtained in 5:95 ratio and **31b** was isolated in 66% (0.194 g) yield as a yellow solid: mp 167-169 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, *J* = 6.9 Hz, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.56 (d, *J* = 5.3 Hz, 1H), 7.38 (dd, *J* = 5.3, 2.3 Hz, 1H), 7.25-7.12 (m, 2H), 7.11-6.99 (m, 2H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.63 (td, *J* = 6.8, 1.2 Hz, 1H).

^{19}F NMR (376 MHz, CDCl$_3$) δ -115.0.

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.4 (d, *J* = 248.0 Hz), 146.2, 135.0, 130.5 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 8.2 Hz), 126.6, 126.1, 124.6, 124.3 (d, *J* = 3.6 Hz), 123.8, 123.4 (d, *J* = 14.7 Hz), 117.8, 117.5, 116.0 (d, *J* = 22.2 Hz), 112.3.

HRMS calcd for [M+H]$^+$ $C_{17}H_{12}FN_2S$ 295.0700, found: 295.0699.

3-(5-Methyl-3-phenylthien-2-yl)imidazo[1,2-*a*]pyrazine (32b)

From 4-(2-bromophenyl)-2-methylthiophene **1m** (0.253 g, 1 mmol) and imidazo[1,2-*a*]pyrazine (0.238 g, 2 mmol), a mixture of **32a** and **32b** was obtained in 9:91 ratio and **32b** was isolated in 71% (0.207 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.09 (d, *J* = 1.5 Hz, 1H), 7.86 (s, 1H), 7.63 (d, *J* = 4.7 Hz, 1H), 7.48 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.24-7.19 (m, 3H), 7.18-7.12 (m, 2H), 7.08 (q, *J* = 1.2 Hz, 1H), 2.61 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 143.8, 142.4, 141.7, 141.1, 136.5, 135.6, 129.5, 129.0, 128.2, 127.7, 127.2, 120.0, 119.3, 117.0, 15.4.

HRMS calcd for [M+H]$^+$ $C_{17}H_{14}N_3S$ 292.0903, found: 292.0902.

2-Ethyl-4-methyl-5-(5-(pyridin-3-yl)-3-(*p*-tolyl)thien-2-yl)thiazole (33)

From 2-ethyl-4-methyl-5-(3-(*p*-tolyl)thien-2-yl)thiazole **4b** (0.299 g, 1 mmol) and 3-bromopyridine (0.316 g, 2 mmol), **33** was isolated in 86% (0.323 g) yield as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 (s, 1H), 8.57 (d, *J* = 3.4 Hz, 1H), 7.90 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.45 (s, 1H), 7.35 dd, *J* = 7.2, 4.8 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 2.14 (s, 3H), 1.39 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.3, 150.4, 148.9, 146.8, 142.5, 140.3, 137.3, 132.7, 132.7, 129.9, 129.4, 128.2, 127.7, 126.5, 123.7, 122.4, 27.0, 21.2, 15.9, 14.1.

HRMS calcd for [M+H]$^+$ $C_{22}H_{21}N_2S_2$ 377.1141, found: 377.1138.

1-(3'-Phenyl-[2,2'-bithiophen]-5-yl)ethan-1-one (34b) and 1-(4'-Phenyl-[2,2'-bithiophen]-5-yl)ethan-1-one (34c)

From 3-phenylthiophene (0.160 g, 1 mmol) and 1-(5-bromothien-2-yl)ethan-1-one (0.410 g, 2 mmol), a mixture of **34b** and **34c** was obtained in 47:53 ratio. Product **34b** was isolated in 8% (0.023 g) yield as a yellow solid: mp 127-129 °C, and product **34c** was isolated in 9% (0.026 g) yield as a yellow solid: mp 121-123 °C.

34b:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, *J* = 3.9 Hz, 1H), 7.43-7.32 (m, 6H), 7.11 (d, *J* = 5.1 Hz, 1H), 6.94 (d, *J* = 3.9 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 190.3, 144.8, 143.4, 140.8, 135.8, 132.6, 131.1, 130.7, 129.2, 128.7, 127.9, 127.0, 125.6, 26.6.

HRMS calcd for [M+H]$^+$ $C_{16}H_{13}OS_2$ 285.0402, found: 285.0403.

34c:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66-7.58 (m, 4H), 7.49-7.41 (m, 3H), 7.39-7.32 (m, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 2.59 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 190.3, 145.6, 143.5, 142.7, 137.0, 135.1, 133.3, 129.0, 127.7, 126.4, 124.7, 124.3, 121.2, 26.6.

HRMS calcd for [M+H]$^+$ $C_{16}H_{13}OS_2$ 285.0402, found: 285.0403.

2-Methyl-2-(3'-phenyl-[2,2'-bithiophen]-5-yl)-1,3-dioxolane (35b)

From 3-(2-bromophenyl)thiophene **1a** (0.239 g 1 mmol) and 2-methyl-2-(thien-2-yl)-1,3-dioxolane (0.340 g, 2 mmol), a mixture of **35a** and **35b** was obtained in 4:96 ratio and **35b** was isolated in 56% (0.184 g) yield as a colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41-7.32 (m, 5H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.09 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 3.7 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 4.08-3.91 (m, 4H), 1.76 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 147.4, 139.0, 136.3, 135.6, 131.6, 130.6, 129.2, 128.4, 127.4, 126.2, 124.2, 124.1, 107.1, 64.9, 27.4.

HRMS calcd for [M+H]$^+$ $C_{18}H_{17}O_2S_2$ 329.0665, found: 329.0665.

Deprotection of **35b** into **34b**: A 2 N aqueous HCl solution (1 mL) was added to a solution of **35b** (0.164 g, 0.5 mmol) in THF (1 mL). The resulting mixture was stirred at 60 °C for 8 h. The mixture was extracted with Et_2O (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give product **34b** in 86% (0.122 g).

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its ESI.

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Notes and references

1. W. Liao, Z. Wang, Y. Han, Y. Qi, J. Liu, J. Xie, Y. Tian, Q. Lei, R. Chen, M. Sun, L. Tang, G. Gong and Y. Zhao, Design, synthesis and biological activity of novel 2,3,4,5-tetrasubstituted thiophene derivatives as PI3Ka inhibitors with potent antitumor activity, *Eur. J. Med. Chem.* 2020, **197**, 112309.
2. K. K.-C. Liu, J. Zhu, G. L. Smith, M.-J. Yin, S. Bailey, J. H. Chen, Q. Hu, Q. Huang, C. Li, Q. J. Li, M. A. Marx, G. Paderes, P. F. Richardson, N. W. Sach, M. Walls, P. A. Wells and A. Zou, Highly Selective and Potent Thiophenes as PI3K Inhibitors with Oral Antitumor Activity, *ACS Med. Chem. Lett.* 2011, **2**, 809-813.
3. X. Wu, Y. Wan, A. K. Mahalingam, A. M. S. Murugaiah, B. Plouffe, M. Botros, A. Karlén, M. Hallberg, N. Gallo-Payet and M. Alterman, Selective Angiotensin II AT2 Receptor Agonists: Arylbenzylimidazole Structure-Activity Relationships, *J. Med. Chem.* 2006, **49**, 7160-7168.
4. W. Wang, S. Zhang, T. Zhang, Y. Yang, Y. Cui, Y. Yu, Y. Xiao, D. H. Ryu, C. E. Song and J. Hou, Molecule Design of Novel Electron Acceptor with Superior Chemical Stability for Photovoltaic Applications, *Adv. Funct. Mater.* 2023, **33**, 2304752.
5. C. Messina, K. McKibbon, K. Shae-Lynn Wong, P. Prevost, V. Petkov, and P. Forgione, A Modular and Regioselective Synthesis of Di- and Triarylated Thiophenes: Strategies for Accessing Challenging Isomeric Motifs, *J. Org. Chem.* 2025 ,**90**, 15595-15611.
6. S.-i. Sakurai, H. Goto and E. Yashima, Synthesis and Chiroptical Properties of Optically Active, Regioregular Oligothiophenes, *Org. Lett.* 2001, **3**, 2379-2382.
7. C. Zhao, Y. Zhang, C. Wang, L. Rothberg and M.-K. Ng, Synthesis of Homopolymer Containing Diphenyl End-Capped Oligothiophene Co-oligomer Unit in the Side Chain, *Org. Lett.* 2006, **8**, 1585-1588.
8. R. Takita, C. Song and T. M. Swager, π-Dimer Formation in an Oligothiophene Tweezer Molecule, *Org. Lett.* 2008, **10**, 5003-5005.
9. D. Schiefer, H. Komber, K. F. Mugwanga, S. Kunz, R. Hanselmann, G. Reiter and M. Sommer, Poly(3-(2,5-dioctylphenyl)thiophene) Synthesized by Direct Arylation Polycondensation: End Groups, Defects, and Crystallinity, *Macromolecules* 2016, **49**, 7230-7237.
10. C. A. Briehn, T. Kirschbaum and P. Baeuerle, Polymer-Supported Synthesis of Regioregular Head-to-Tail-Coupled Oligo(3-arylthiophene)s Utilizing a Traceless Silyl Linker, *J. Org. Chem.* 2000, **65**, 352-359.
11. E. Naudin, N. El Mehdi, C. Soucy, L. Breau and D. Belanger, Poly(3-arylthiophenes): Syntheses of Monomers and Spectroscopic and Electrochemical Characterization of the Corresponding Polymers, *Chem. Mat.* 2001, **13**, 634-642.
12. P. B. Arockiam, C. Bruneau and P. H. Dixneuf, Ruthenium(II)-catalyzed C–H bond activation and functionalization, *Chem. Rev.* 2012, **112**, 5879-5918.
13. L. Theveau, C. Schneider, C. Fruit and C. Hoarau, Orthogonal palladium-catalyzed direct C−H bond arylation of heteroaromatics with aryl halides, *ChemCatChem* 2016, **8**, 3183-3194.
14. S. Ruiz, P. Villuendas and E. P. Urriolabeitia, Ru-catalysed C–H functionalisations as a tool for selective organic synthesis, *Tetrahedron Lett.,* 2016, **57**, 3413-3432.
15. T. Gensch, M. J. James, T. Dalton and F. Glorius, Increasing catalyst efficiency in C−H activation catalysis, *Angew. Chem. Int. Ed.* 2018, **57**, 2296-2306.
16. J. Kalepu, P. Gandeepan, L. Ackermann and L. T. Pilarski, C4–H indole functionalisation: precedent and prospects, *Chem. Sci.* 2018, **9**, 4203-4216.
17. K. Hirano and M. Miura, A lesson for site-selective C–H functionalization on 2-pyridones: radical, organometallic, directing group and steric controls, *Chem. Sci.* 2018, **9**, 22-32.
18. S. Mao, H. Li, X. Shi, J.-F. Soulé and H. Doucet, Environmentally benign arylations of 5-membered ring heteroarenes by Pd-catalyzed C−H bonds activations, *ChemCatChem* 2019, **11**, 269-286.
19. S. Rej, Y. Ano and N. Chatani, Bidentate directing groups: An efficient tool in C−H bond functionalization chemistry for the expedient construction of C−C bond, *Chem. Rev.* 2020, **120**, 1788-1887.
20. J. H. Docherty, T. M. Lister, G. Mcarthur, M. T. Findlay, P. Domingo-Legarda, J. Kenyon, S. Choudhary and I. Larrosa, Transition-Metal-Catalyzed C–H Bond Activation for the Formation of C–C Bonds in Complex Molecules, *Chem. Rev.* 2023, **123**, 7692-7760.
21. Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara and M. Shimizu, Palladium-catalyzed coupling reaction of chloropyrazines with indole, *Heterocycles* 1985, **23**, 2327-2333.
22. A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani and Y. Aoyagi, Palladium-catalyzed arylation of furan, thiophene, benzo[*b*]furan and benzo[*b*]thiophene, *Heterocycles* 1990, **31**, 1951-1958.
23. K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita and T. Ikeda, Syntheses and properties of donor−acceptor-type 2,5-diarylthiophene and 2,5-diarylthiazole, *Org. Lett.* 2004, **6**, 2011-2014.
24. E. David, S. Pellet-Rostaing and M. Lemaire, Heck-like coupling and Pictet–Spengler reaction for the synthesis of

benzothieno[3,2-*c*]quinolines, *Tetrahedron* 2007, **63**, 8999-9006.

25. J. Roger, F. Požgan and H. Doucet, Ligand-less palladium-catalyzed direct 5-arylation of thiophenes at low catalyst loadings, *Green Chem.* 2009, **11**, 425-432.
26. B. Liégault, I. Petrov, S. I. Gorlesky and K. Fagnou, Modulating reactivity and diverting selectivity in palladium-catalyzed heteroaromatic direct arylation through the use of a chloride activating/blocking group, *J. Org. Chem.* 2010, **75**, 1047-1060.
27. H.-Y. Huang, A. Benzai, X. Shi and H. Doucet, Effective tools for the metal-catalyzed regiodivergent direct arylations of (hetero)arenes, *Chem. Rec.* 2021, **21**, 343-356.
28. Y. Li, J. Wang, M. Huang, Z. Wang, Y. Wu and Y. Wu, Direct C–H Arylation of Thiophenes at Low Catalyst Loading of a Phosphine-Free Bis(alkoxo)palladium Complex, *J. Org. Chem.* 2014, **79**, 2890-2897.
29. S. Ma and Z. Gu, 1,4-Migration of rhodium and palladium in catalytic organometallic reactions, *Angew. Chem. Int. Ed.* 2005, **44**, 7512-7517.
30. X. Dong, H. Wang, H. Liu and F. Wang, Recent advances in transition metal migration involving reactions, *Org. Chem. Front.* 2020, **7**, 3530-3556.
31. M.-Y. Li, D. Wei, C.-G. Feng and G.-Q. Lin, Tandem Reactions involving 1,4-Palladium Migrations, *Chem. Asian J.* 2022, **17**, e202200456.
32. R. C. Larock, Y. D. Lu, A. C. Bain and C. E. Russell, Palladium-catalyzed coupling of aryl iodides, nonconjugated dienes and carbon nucleophiles by palladium migration, *J. Org. Chem.* 1991, **56**, 4589-4590.
33. M. A. Campo, H. Zhang, T. Yao, A. Ibdah, R. D. McCulla, Q. Huang, J. Zhao, W. S. Jenks and R. C. Larock, Aryl to aryl palladium migration in the Heck and Suzuki coupling of *o*-halobiaryls, *J. Am. Chem. Soc.* 2007, **129**, 6298-6307.
34. L. Liu, M. Cordier, T. Roisnel and H. Doucet, 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, *Org. Chem. Front.* 2023, **10**, 1441-1455.
35. M. A. Campo and R. C. Larock, Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Cyclocarbonylation of *o*-Halobiaryls, *J. Org. Chem.* 2002, **67**, 5616-5620.
36. W. Hagui, N. Besbes, E. Srasra, T. Roisnel, J.-F. Soule and H. Doucet, Short Synthesis of Sulfur Analogues of Polyaromatic Hydrocarbons through Three Palladium-Catalyzed C–H Bond Arylations, *Org. Lett.* 2016, **18**, 4182-4185.
37. T. Cantat, E. Génin, C. Giroud, G. Meyer and A. Jutand, Structural and kinetic effects of chloride ions in the palladium catalyzed allylic substitutions, *J. Organomet. Chem.* 2003, **687**, 365-376.
38. A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto and T. Ikeda, Facile synthesis of 2,5-diarylthiazoles via palladium-catalyzed tandem C–H substitutions. Design of tunable light emission and liquid crystalline characteristics, *J. Am. Chem. Soc.* 2003, **125**, 1700-1701.
39. A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, Palladium-catalyzed direct arylation of thiazoles with aryl bromides, *Tetrahedron* 2003, **59**, 5685-5689.
40. J. J. Dong, J. Roger, C. Verrier, T. Martin, R. Le Goff, C. Hoarau and H. Doucet, Carbonates: eco-friendly solvents for palladium-catalysed direct arylation of heteroaromatics, *Green Chem.* 2010, **12**, 2053-2063.
41. D. L. Davies, S. M. A. Donald and S. A. Macgregor, Computational study of the mechanism of cyclometalation by palladium acetate, *J. Am. Chem. Soc.* 2005, **127**, 13754-13755.
42. M. Lafrance and K. Fagnou, Palladium-catalyzed benzene arylation: Incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design, *J. Am. Chem. Soc.* 2006, **128**, 16496-16497.
43. S. I. Gorelsky, Origins of regioselectivity of the palladium-catalyzed (aromatic)C-H bond metalation–deprotonation, *Coord. Chem. Rev.* 2013, **257**, 153-164.
44. D. L. Davies, S. A. Macgregor and C. L. McMullin, Computational studies of carboxylate-assisted C-H activation and functionalization at group 8-10 transition metal centers, *Chem. Rev.* 2017, **117**, 8649-8709.
45. M. Kienle, A. Unsinn and P. Knochel, Synthesis of Dibenzothiophenes and Related Classes of Heterocyclesby Using Functionalized Dithiocarbamates, *Angew. Chem. Int. Ed.* 2010, **49**, 4751-4754.

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Data availability

The data underlying this study are available in the published article and its ESI.