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Palladium-catalyzed selective decarboxylative coupling reaction versus direct C—H arylation for arylation of heteroaromatics

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Conditions for selective palladium-catalyzed decarboxylative 2-arylation of 3-substituted thiophene and furan derivatives bearing an ester at C2 position have been established. By using 2 mol% phosphine-free $Pd(OAc)_2$ as the catalyst and a mixture of KOH and K_2CO_3 as the bases, in dimethylacetamide, moderate to good yields of the desired 2-arylated products were obtained. A range of functional groups such as nitrile, nitro, formyl or acetyl on the aryl bromides was tolerated. This method allows us to employ in some cases more convenient reactants in terms of cost or physical properties (boiling point) for arylations. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: palladium; catalysis; thiophenes; furans; arylation; decarboxylative coupling

Introduction

2-Arylated thiophenes and furans continue to attract the attention of synthetic organic chemists due to the biological properties of some of these derivatives. For example, raloxifene is a drug used to prevent and treat osteoporosis, dantrolene is a muscle relaxant, and lapatinib is employed against breast cancer (Fig. 1).

Traditional methods for arylations of thiophenes or furans are the metal-catalyzed Suzuki, Negishi, Stille or Kumada cross-coupling reactions.[1] However, these methods required preliminary synthesis of organometallic compounds, and stoichiometric amount of metal salts were produced as by-products. In this context, the catalytic direct C—H arylation provides a cost-effective and environmentally attractive method for the synthesis of such compounds.[2,3] However, the control of the regioselectivity remains an essential issue due to the presence of several C—H bonds with similar reactivity on several heterocycles. For example, the direct arylation of 3-substituted thiophenes or furans to provide the mono-2-arylated products are less effective owing to the presence of two reactive positions C2 and C5.[4–10] In 2003, Sharp and co-workers demonstrated that the use of Pd$(PPh_3)_4$ in toluene allowed the regioselective arylation at the 2-position of methyl 3-thiophene carboxylate.[4] The reactivity of 3-methoxythiophene for direct C—H arylation was explored by Borghese and co-workers. They obtained selectively the 2-arylated thiophenes in 28–60% yields.[5] On the other hand, Bilodeau and co-workers reported that a mixture of the 2- and 5-phenylated thiophenes in a 3.3:1 ratio was obtained by using $Pd[P(tBu)_3]_2$ as the catalyst for the arylation of 3-methylthiophene.[6] Similarly, we have reported examples of palladium-catalyzed arylation of 3-formylthiophene, in which the 2-arylated thiophenes were produced in 76–86% regioselectivity, together with 5-arylated thiophenes.[7,8] In 2011, Mori and co-workers reported that the reaction of 3-hexylthiophene with 4-bromotoluene also gives a mixture of the C2- and C5-monoarylated thiophenes as well as the C2,C5-diarylated thiophene.[9] Therefore, there is still room for improving the regioselectivity for a selective access to 2-arylated 3-substituted thiophenes or furans.

Since the pioneering studies of Myers and Goossen,[11,12] using carboxylic *acids* as cross-coupling partners for metal-mediated decarboxylation reactions, several exciting results on this research area have been reported.[13,14] However, little is known on the reactivity of heteroarenes bearing an *ester* at C2 for decarboxylation versus direct arylation reactions. From this consideration, we decided to explore the reactivity of two types of five-membered ring heteroarenes bearing an ester at C2: methyl 3-chlorothiophene-2-carboylate and methyl 3-methylfuran-2-carboxylate. They were used as model substrates to evaluate the regioselectivity of the arylation and to determine conditions for the selective decarboxylative coupling at C2.

Results and Discussion

The reaction of 1-bromonaphthalene with 2 equiv. of methyl 3-chlorothiophene-2-carboxylate was employed as the model reaction for the optimization of the conditions (Scheme 1 and Table 1). Based on our previously established conditions for decarboxylative arylation of 2-arylfuroates,[15] we performed the reaction at 150°C in the presence of a mixture of 2 equiv. of KOH associated with 2 equiv. of another base. Initially, the reaction was carried out in dimethylacetamide (DMA) with

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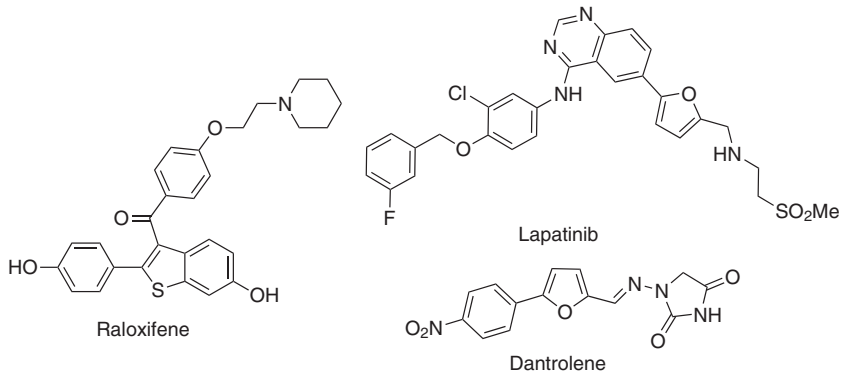
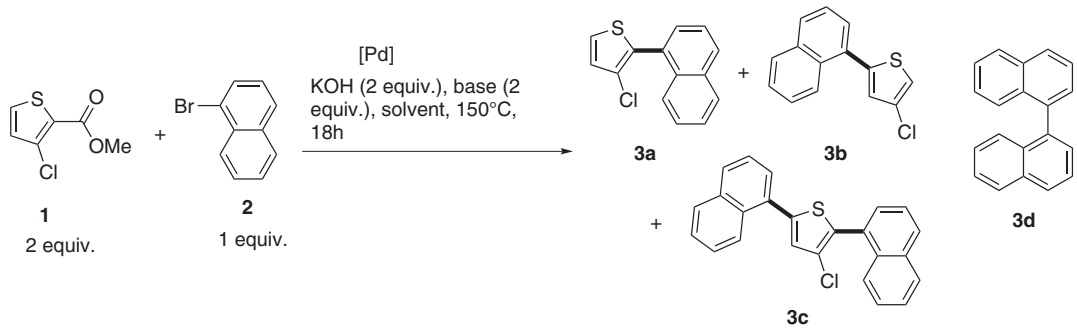


Figure 1. Examples of bioactive thiophene or furan derivatives.



Scheme 1. Palladium-catalyzed arylation of methyl 3-chlorothiophene-2-carboxylate with 1-bromonaphthalene.

1 mol% of $PdCl(C_3H_5)(dppb)$ [dppb: 1,4-bis(diphenylphosphino) butane][16] as the catalyst. With K_2CO_3 or KOAc as the second base, the 1-bromonaphthalene was completely converted, with about 11% and 16% naphthalene-homocoupling by-product **3d** produced, respectively, and more than 80% yields of arylation products **3a** and **3b** were obtained in both cases (Table 1, entries 1 and 2). Only trace amounts of 2,5-diarylated product **3c** were detected. Although the competing formation of 2- or 5-arylation products coexists, the decarboxylative arylation at C2 position to form **3a** prevailed over the direct C—H arylation at C5 to give **3b**. However, the amount of C5 arylation product **3b** was significant, as it was produced in 18% and 24% yields, respectively. Interestingly, K_2CO_3 as the second base seems to be more beneficial for the decarboxylative arylation at C2 position than KOAc. 1-Bromonaphthalene conversion decreased when $Pd(OAc)_2$ was employed in place of $PdCl(C_3H_5)(dppb)$ as the catalyst, but the regioselectivity was improved with an increase of the C2:C5 ratio from 3.6 to 7.4 (Table 1, entries 1 and 4). Therefore, in the subsequent experiments, $Pd(OAc)_2$ was selected as the catalyst and K_2CO_3 as the second base. Increasing the $Pd(OAc)_2$ loading from 1% to 2 mol% enhanced the 1-bromonaphthalene conversion from 75% to 90% (Table 1, entries 4 and 5). Further optimization of the condition revealed that both Cs_2CO_3 and CsOAc as the second base resulted in relatively lower conversions with about 44–79% substrate recovery. Again, the carbonate base proved to be more effective than acetate, affording a C2:C5 ratio of 3.0 versus 0.7 with CsOAc. The solvent nature usually plays an important role for such reactions. Employing the non-polar solvent xylene failed to give any substrate conversion (Table 1, entry 8). Although full conversion was obtained with DMF as the solvent, a large amount of homocoupling 1-bromonaphthalene **3d** by-product was formed (Table 1, entry 9). It should be noted that, in all cases, no cleavage of the C—Cl thiophene bond was detected. Consequently, we employed the following conditions for the subsequent reactions: 2 mol% $Pd(OAc)_2$ as the catalyst, a mixture of 2 equiv. of KOH and 2 equiv. of K_2CO_3 as the bases, DMA as the solvent, at 150°C.

Having the decarboxylation reaction conditions in hand, we next explored the scope of this protocol (Tables 2 and 3). Firstly, the influence of the nature of the aryl bromides for coupling with methyl 3-chlorothiophene-2-carboxylate was investigated (Table 2). The system proved to be tolerant to several functional groups. 4-Bromobenzonitrile, 4-bromoacetophenone, 4-bromobenzaldehyde and 4-bromonitrobenzene were successfully coupled with methyl 3-chlorothiophene-2-carboxylate, giving the corresponding C2-arylated products **4a–7a** in moderate to good yields, from 44% to 66%, with ratios of C2:C5 arylations from 8.8 to 14.5 (Table 2, entries 1–4). The use of electron-rich aryl bromide, 4-*tert*-butylbromobenzene, led to a lower conversion of 43%. It is noteworthy that, although only 30% yield of desired product **8a** was obtained, a relatively high regioselectivity could be achieved with a ratio C2:C5 of 10 (Table 2, entry 5). Selective 2-arylations were also observed using 2-bromonaphthalene and 9-bromoanthracene, resulting in 58% and 73% yields of the products **9a**, **11a** respectively (Table 2, entries 6 and 8). The *ortho*-substituted aryl bromide, 2-bromobenzonitrile, is less selective for decarboxylative arylation at the C2 position, as a 48:19 ratio of C2:C5-arylated products **10a** and **10b** was obtained (Table 2, entry 7). Pyridines or quinolines are π-electron-deficient heterocycles and therefore their oxidative addition to the palladium is, in general, relatively easy. From such heteroaryl bromides, a similar reactivity to that of the electron-deficient aryl bromides was expected. As anticipated, using 3- or 4-bromopyridines, 3-bromoquinoline and 4-bromoisoquinoline, the decarboxylative coupling products

Table 1. Influence of the reaction conditions for palladium-catalysed arylation of methyl 3-chlorothiophene-2-carboxylate with 1-bromonaphthalene (Scheme 1)

Entry	Catalyst (mol%)	Second base	Solvent	Conv. (%)	Yield **3a** (%)	Yield **3b** (%)	Ratio **3a**/**3b**
1	$PdCl(C_3H_5)(dppb)$ (1)	K_2CO_3	DMA	100	65	18	3.6
2	$PdCl(C_3H_5)(dppb)$ (1)	KOAc	DMA	100	64	24	2.6
3	$Pd(OAc)_2$ (1)	KOAc	DMA	92	71 (61)	21	3.4
4	$Pd(OAc)_2$ (1)	K_2CO_3	DMA	75	52	7	7.4
5	$Pd(OAc)_2$ (2)	K_2CO_3	DMA	90	61	6	10.1
6	$Pd(OAc)_2$ (2)	Cs_2CO_3	DMA	56	21	7	3.0
7	$Pd(OAc)_2$ (2)	CsOAc	DMA	21	8	11	0.7
8	$Pd(OAc)_2$ (2)	KOAc	xylene	0	—	—	—
9	$Pd(OAc)_2$ (2)	K_2CO_3	DMF	100	43	5	8.6

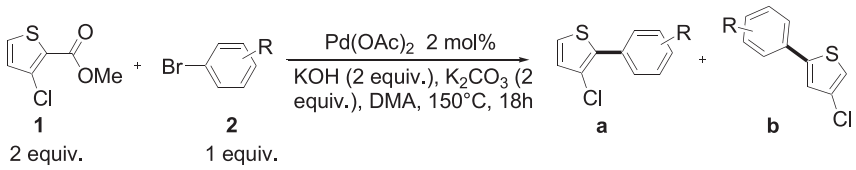
Conditions: 1-bromonaphthalene (1 mmol), methyl 3-chlorothiophene-2-carboxylate (2 mmol), KOH (2 mmol), second base (2 mmol), 150°C, 18 h, argon, conversion of 1-bromonaphthalene, gas chromatographic and NMR yields; yield in parenthesis is isolated.

12a–15a were obtained as the major products in 50–89% yields (Table 2, entries 9–12). Compared with 3- or 4-bromopyridines, 3-bromoquinoline or 4-bromoisoquinoline was expected to give lower regioselectivities towards C2 arylation due to their steric hindrance. To our surprise, they exhibited unexpectedly higher C2:C5 ratios of 17.6 and 22.2, respectively (Table 2, entries 11 and 12). For comparison, we also carried out the direct C—H arylation reaction starting from 3-chlorothiophene and 4-bromoisoquinoline. In this case, a lower C2:C5 ratio of 8 was obtained (Table 2, entry 13). These results confirm that the presence of the carboxylate group at the C2 position seems advantageous for improving the regioselectivity towards C2 arylations.

To evaluate the substrate scope with respect to the heteroarene, the reactivity of methyl 3-methylfuran-2-carboxylate was examined (Fig. 2 and Table 3). The use of this substrate, instead of 3-methylfuran, for the synthesis of 2-arylated 3-methylfurans is particularly attractive as: (i) the much higher boiling point for methyl 3-methylfuran-2-carboxylate than for 3-methylfuran (b.p. 195°C vs. 65°C) allows reactions to be carried out in classical glassware instead of autoclaves; (ii) methyl 3-methylfuran-2-carboxylate is available at a more affordable cost than 3-methylfuran.

We were pleased to find that, again, the desired 2-arylated products **16–21** were regioselectively obtained in all cases. With this substrate, it should be noted that no significant amounts of C5-arylation products were detected by gas chromatographic–mass spectrometric analysis of the crude mixtures. The products **16–21** were obtained in moderate to good yields ranging from 49% to 72% using 2 mol% $Pd(OAc)_2$ catalyst. Again, the reaction tolerates electron-withdrawing substituents, congested aryl bromides or pyridyl bromides.

Table 2. Scope of the palladium-catalyzed decarboxylative coupling of methyl 3-chlorothiophene-2-carboxylate with aryl bromides

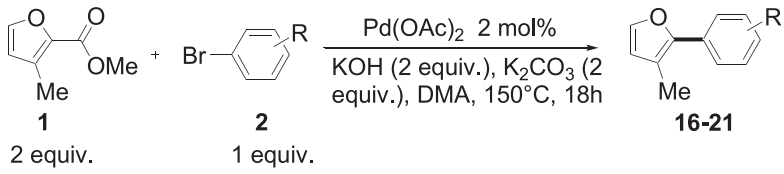


Entry	Aryl bromide or R	Conv. (%)	Yield in 2-arylated product **a** (%)	Ratio **a**/**b**
1	4-CN	100	**4a** 58	11.6
2	4-COMe	100	**5a** 44	8.8
3	4-CHO	100	**6a** 58	14.5
4	4-NO_2	93	**7a** 66	13.2
5	4-*t*Bu	43	**8a** 30	10
6	2-Bromonaphthalene	81	**9a** 58	11.6
7	2-CN	100	**10a** 48	2.5
8	9-Bromoanthracene	100	**11a** 73	6.1
9	4-Bromopyridine, hydrochloride	100	**12a** 60	15
10	3-Bromopyridine	89	**13a** 50	5
11	3-Bromoquinoline	100	**14a** 88	17.6
12	4-Bromoisoquinoline	100	**15a** 89	22.2
13	4-Bromoisoquinoline	100	**15a** 88	8[a]

Conditions: $Pd(OAc)_2$ (0.02 mmol), aryl bromide (1 mmol), methyl 3-chlorothiophene-2-carboxylate (2 mmol), KOH (2 mmol), KOAc (2 mmol), 18h, 150°C, conversion of the aryl bromide.

[a]$Pd(OAc)_2$ (0.1 mmol), 4-bromoisoquinoline (1 mmol), 3-chlorothiophene (2.0 mmol), KOAc (2 mmol), 18 h, 130°C.

Table 3. Scope of the palladium-catalysed decarboxylative coupling of methyl 3-methylfuran-2-carboxylate with aryl bromides



Entry	Aryl bromide or R	Conv. (%)	Yield in 2-arylated product (%)
1	4-NO_2	100	**16** 49
2	1-Bromonaphthalene	100	**17** 50
3	9-Bromoanthracene	100	**18** 72
4	4-Bromopyridine, hydrochloride	100	**19** 59
5	3-Bromoquinoline	100	**20** 50
6	4-Bromoisoquinoline	76	**21** 52

Conditions: $Pd(OAc)_2$ (0.02 mmol), aryl bromide (1 mmol), methyl 3-methylfuran-2-carboxylate (2 mmol), KOH (2 mmol), KOAc (2 mmol), 18h, 150°C, conversion of the aryl bromide.

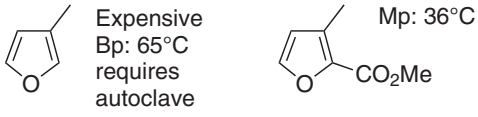


Figure 2. Reactions with 3-methylfuran-2-carboxylate do not require use of autoclaves.

Conclusion

We have investigated the palladium-catalyzed decarboxylative coupling reaction versus direct arylation of 3-substituted thiophene- or furan-2-carboxylates. We found that, using a mixture of KOH and K_2CO_3 as the bases in DMA with 2 mol% $Pd(OAc)_2$ as the catalyst and under argon atmosphere at 150°C, a decarboxylative arylation reaction occurred preferentially to give the C2-arylated products. With various aryl bromides, the desired 2-arylated products were obtained in moderate to good yields. These results demonstrated that these heteroaryl 2-carboxylates can be employed as the coupling partners for selective palladium-catalyzed 2-arylation of heteroarenes. Owing to the higher boiling point of the ester-substituted heteroarenes, the handling of some of these heteroarenes is more convenient. Finally, this strategy proved to display a good functional group tolerance on the aryl bromide coupling partner.

Experimental

General

All reactions were run under argon in Schlenk tubes using vacuum lines. DMA, DMF or xylene, analytical grade, were not distilled before use. The bases Cs_2CO_3, CsOAc, K_2CO_3, KOAc and $Pd(OAc)_2$ were used as received. Commercial aryl bromides, methyl 3-chlorothiophene-2-carboxylate and methyl 3-methylfuran-2-carboxylate were used without purification. ^1H and ^{13}C spectra were recorded with a Bruker 400 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography was performed on silica gel (230–400 mesh).

Preparation of the $PdCl(C_3H_5)(dppb)$ catalyst[16]

An oven-dried 40 ml Schlenk tube equipped with a magnetic stirring bar under argon atmosphere was charged with $[Pd(C_3H_5)Cl]_2$ (0.182 g, 0.5 mmol) and dppb (0.426 g, 1 mmol). Anhydrous dichloromethane (10 ml) was added, and the solution was stirred at room temperature for 20 min. The solvent was removed under vacuum. The yellow powder obtained was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General Procedure for Coupling Reactions

In a typical experiment, the aryl bromide (1 mmol), methyl 3-chlorothiophene-2-carboxylate (0.354 g, 2 mmol) or methyl 3-methylfuran-2-carboxylate (0.280 g, 2 mmol), KOH (0.112 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and $Pd(OAc)_2$ (see tables) were dissolved in DMA (3 ml) under an argon atmosphere. The reaction mixture was stirred at 150°C (see tables) for 16 h. The solution was diluted with water (15 ml) and the product was then extracted three times with ethyl acetate or dichloromethane. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuum. The products were purified by silica gel column chromatography.

*3-Chloro-2-(1-naphthyl)thiophene (**3a**)*

^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.88 (m, 2H, CCC***H***CHCHC***H***), 7.79 (d, J = 7.7 Hz, 1H, CCHCHC***H***C), 7.58-7.45 (m, 4H, CC***H***C***H***CHCCHC***H***C***H***CHC), 7.41 (d, J = 5.3 Hz, 1H, SC***H***), 7.09 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4 (S***C***CCl), 133.6 (CCHCHCH***C***), 132.1 (***C***CHCHCHC), 129.4 (CCHCHCHC***C***HCHCH***C***H), 129.3 (C***C***CCHCHCHCH), 128.3 (CCHCH***C***HCCHCHCH), 128.0 (SCH***C***H), 126.5 (S***C***HCH), 126.1 (CCH***C***HCHCCHCHCH), 126.0 (C***C***HCHCHCCHCHCH), 125.1 (CCHCHCHCCH***C***H***C***HCH), 124.2 (***C***—Cl). Elemental analysis: calcd (%) for $C_{14}H_9ClS$ (244.74): C 68.71, H 3.71; found: C 68.88, H 3.94.

*3-Chloro-2,5-di(1-naphthyl)thiophene (**3c**)*

This compound was obtained in low yield.

^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 7.7 Hz, 1H, naphthyl), 8.03 (d, J = 7.7 Hz, 1H, naphthyl), 8.00–7.88 (m, 4H, naphthyl), 7.70–7.65 (m, 2H, naphthyl), 7.64–7.50 (m, 6H, naphthyl), 7.31 (s, 1H, thiophene). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3 (S***C***C), 134.6

(Ar), 133.9 (Ar), 133.7 (Ar), 132.0 (Ar), 131.4 (Ar), 131.3 (Ar), 129.5 (Ar), 129.4 (naphthyl ***C***H), 129.2 (Ar), 129.0 (naphthyl ***C***H), 128.5 (naphthyl ***C***H), 128.4 (naphthyl ***C***H), 128.1 (naphthyl ***C***H), 127.8 (naphthyl ***C***H), 126.8 (naphthyl ***C***H), 126.6 (naphthyl ***C***H), 126.3 (naphthyl ***C***H), 126.2 (naphthyl ***C***H), 126.1 (naphthyl ***C***H), 125.4 (naphthyl ***C***H), 125.3 (naphthyl ***C***H), 125.1 (naphthyl ***C***H), 123.7 (SC***C***H).

*4-(3-Chlorothiophen-2-yl)-benzonitrile (**4a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 2H, C***H***CHCCN), 7.63 (d, J = 7.5 Hz, 2H, CHC***H***CCN), 7.29 (d, J = 5.3 Hz, 1H, SC***H***CH), 6.97 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8 (***C***-1′ on phenyl), 133.9 (S***C***CCl), 132.4 (CH***C***HCCN), 129.8 (SCH***C***H), 128.9 (***C***HCHCCN), 125.5 (SCH***C***H), 123.0 (S***C***H), 118.6 (***C***N), 111.4 (***C***HCN). Elemental analysis: calcd (%) for $C_{11}H_6ClNS$ (219.69): C 60.14, H 2.75; found: C 60.07, H 2.87.

*2-(4-Acetylphenyl)-3-chlorothiophene (**5a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.5 Hz, 2H, CHC***H***CCOCH$_3$), 7.72 (d, J = 7.5 Hz, 2H, C***H***CHCCOCH$_3$), 7.27 (d, J = 5.3 Hz, 1H, SC***H***), 6.96 (d, J = 5.3 Hz, 1H, SCHC***H***), 2.56 (s, 3H, COC***H$_3$***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0 (***C***OMe), 136.8 (***C***-1′ on phenyl), 136.2 (S***C***CCl), 134.9 (***C***COCH$_3$), 129.7 (SCH***C***H), 128.8 (CH***C***HCCOCH$_3$), 128.7 (***C***HCHCCOCH$_3$), 125.0 (S***C***HCH$_2$), 122.5 (SC***C***Cl), 26.0 (CO***C***H$_3$). Elemental analysis: calcd (%) for $C_{12}H_9ClOS$ (236.72): C 60.89, H 3.83; found: C 60.99, H 3.74.

*2-(4-Formylphenyl)-3-chlorothiophene (**6a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H, C***H***O), 7.88 (d, J = 8.5 Hz, 2H, CHC***H***CCHO), 7.79 (d, J = 8.5 Hz, 2H, C***H***CHCCHO), 7.29 (d, J = 5.3 Hz, 1H, SC***H***), 6.97 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6 (***C***HO), 138.2 (***C***-1′ on phenyl), 135.4 (S***C***CCl), 134.7 (***C***CHO), 130.0 (CH***C***HCCHO), 129.8 (SCH***C***H), 129.0 (***C***HCHCCHO), 125.4 (S***C***H), 122.9 (S***C***CCl). Elemental analysis: calcd (%) for $C_{11}H_7ClOS$ (222.69): C 59.33, H 3.17; found: C 59.27, H 3.29.

*2-(4-Nitrophenyl)-3-chlorothiophene (**7a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.5 Hz, 2H, CHC***H***CNO$_2$), 7.78 (d, J = 8.5 Hz, 2H, C***H***CHCNO$_2$), 7.32 (d, J = 5.3 Hz, 1H, SC***H***), 6.99 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 (***C***NO$_2$), 138.7 (***C***-1′ on phenyl), 133.5 (S***C***CCl), 130.0 (SCH***C***H), 129.1 (***C***HCHCNO$_2$), 125.9 (S***C***HCH), 123.9 (CH***C***HCNO$_2$), 123.5 (SC***C***Cl). Elemental analysis: calcd (%) for $C_{10}H_6ClNO_2S$ (239.68): C 50.11, H 2.52; found: C 50.04, H 2.41.

2-(4-tert-Butylphenyl)-3-chlorothiophene (**8a**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 2H, C***H***CHC^{t}Bu), 7.37 (d, J = 7.5 Hz, 2H, CHC***H***C^{t}Bu), 7.16 (d, J = 5.3 Hz, 1H, SCHC***H***), 6.90 (d, J = 5.3 Hz, 1H, SC***H***CH), 1.28 (s, 9H, ***t*Bu**). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (***C***^{t}Bu), 136.3 (S***C***CCl), 129.3 (***C***-1′ on phenyl), 129.2 (SCH***C***H), 128.3 (***C***HCHC^{t}Bu), 125.6 (S***C***HCH), 123.5 (CH***C***HC^{t}Bu), 121.0 (SC***C***Cl), 34.7 (***C***tBu), 31.3 (—C(***C***H$_3$)$_3$). Elemental analysis: calcd (%) for $C_{14}H_{15}ClS$ (250.79): C 67.05, H 6.03; found: C 67.00, H 5.89.

*3-Chloro-2-(2-naphthyl)thiophene (**9a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, CC***H***CCHCH), 7.80–7.62 (m, 4H, CCHCC***H***CHCHC***H***CC***H***C***H***), 7.40–7.35 (m, 2H, CCHCCHC***H***C***H***CHCCHCH), 7.16 (d, J = 5.3 Hz, 1H, SC***H***), 6.90 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2 (S***C***CCl), 133.2 (CCH***C***CCHCH), 132.8 (***C***CHCCCHCH), 129.7 (CCHC***C***HCH), 129.4 (CCH***C***HCC), 128.3 (CCHCHC***C***HCH), 128.2 (CCHC***C***HCH), 127.8 (SCH***C***H), 127.7 (S***C***HCH), 126.6 (CCHCHCCH***C***H), 126.5 (CCHCCH***C***H), 126.4 (C***C***HCCHCH), 124.1 (C***C***HCHC), 121.2 (SC***C***Cl). Elemental analysis: calcd (%) for $C_{14}H_9ClS$ (244.74): C 68.71, H 3.71; found: C 68.71, H 3.58.

*2-(3-Chlorothiophen-2-yl)-benzonitrile (**10a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.9 Hz, 1H, CC***H***CHCH), 7.59 (t, J = 7.5 Hz, 1H, CCHC***H***CH), 7.50 (d, J = 7.9 Hz, 1H, CNCC***H***CH), 7.46 (t, J = 7.5 Hz, 1H, CNCCHC***H***), 7.35 (d, J = 5.3 Hz, 1H, SC***H***), 6.9 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6 (S***C***CCl), 133.5 (CCH***C***HCH), 132.5 (CNC***C***HCH), 131.9 (CNCCH***C***H), 131.7 (***C***CCN), 128.9 (C***C***HCHCH), 128.5 (SCH***C***H), 126.2 (S***C***HCH), 124.9 (SC***C***Cl), 117.7 (C***C***N), 113.8 (***C***HCN). Elemental analysis: calcd (%) for $C_{11}H_6ClNS$ (219.69): C 60.14, H 2.75; found: C 60.31, H 2.88.

*2-(9-Anthryl)-3-chlorothiophene (**11a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H, CHCC***H***CCH), 7.95 (d, J = 8.0 Hz, 2H, CHC***H***CCHCC***H***CH), 7.63 (d, J = 8.0 Hz, 2H, CHC***H***CCCC***H***CH), 7.47 (d, J = 5.3 Hz, 1H, SC***H***CH), 7.40–7.32 (m, 4H, C***H***C***H***CHCCCCHC***H***C***H***), 7.13 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5 (S***C***CCl), 131.7 (CHCHC***C***HCCHCH), 131.3 (Ar), 128.9 (SCH***C***H), 128.6 (Ar), 128.0 (S***C***HCH), 126.4 (Ar), 126.3 (Ar), 126.1 (Ar), 126.0 (Ar), 125.4 (Ar), 125.2 (SC***C***Cl). Elemental analysis: calcd (%) for $C_{18}H_{11}ClS$ (294.80): C 73.34, H 3.76; found: C 73.50, H 3.59.

*4-(3-Chlorothiophen-2-yl)-pyridine (**12a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 4.8 Hz, 2H, C***H***N), 7.56 (d, J = 4.8 Hz, 2H, C***H***CHN), 7.31 (d, J = 5.3 Hz, 1H, SC***H***), 6.98 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (***C***HN), 139.8 (***C***-1′ on pyridyl), 133.0 (S***C***CCl), 130.1 (SCH***C***H), 125.7 (S***C***H), 123.6 (SC***C***Cl), 122.3 (***C***HCHN). Elemental analysis: calcd (%) for C_9H_6ClNS (195.67): C 55.24, H 3.09; found: C 55.14, H 3.04.

*3-(3-Chlorothiophen-2-yl)-pyridine (**13a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H, CC***H***N), 8.53 (d, J = 4.8 Hz, 1H, NC***H***CH), 7.93 (d, J = 7.9 Hz, 1H, CC***H***CHCHN), 7.30 (dd, J = 7.9, 4.8 Hz, 1H, CCHC***H***CHN), 7.28 (d, J = 5.3 Hz, 1H, SC***H***), 6.98 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3 (C***C***HN), 149.0 (NCHC***H***), 135.8 (C***C***HCHCHN), 132.4 (S***C***CCl), 129.5 (S***C***HCH), 128.5 (***C***CHCHCHN), 125.0 (SCH***C***H), 123.3 (CCH***C***HCHN), 122.8 (SC***C***Cl). Elemental analysis: calcd (%) for C_9H_6ClNS (195.67): C 55.24, H 3.09; found: C 55.08, H 3.32.

*3-(3-Chlorothiophen-2-yl)-quinoline (**14a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H, CC***H***NC), 8.32 (s, 1H, CC***H***C), 8.04 (d, J = 8.0 Hz, 1H, NCC***H***CH), 7.76 (d, J = 8.0 Hz, 1H, CCHCC***H***CH), 7.64 (t, J = 7.9 Hz, 1H, NCCHCHC***H***CH), 7.48 (t, J = 7.9 Hz, 1H, NCCHCHCHC***H***), 7.26 (d, J = 5.3 Hz, 1H, SC***H***), 6.98 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7 (Ar), 147.2 (Ar), 136.9 (Ar), 134.4 (Ar), 125.3 (Ar), 123.4 (Ar), 123.0 (Ar), 121.0 (Ar), 118.6 (Ar), 113.4 (Ar). Elemental analysis: calcd (%) for $C_{13}H_8ClNS$ (245.73): C 63.54, H 3.28; found: C 63.67, H 3.18.

*4-(3-Chlorothiophen-2-yl)-isoquinoline (**15a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H, CCHNC***H***CCH), 8.55 (s, 1H, CC***H***NCHCCH), 8.02 (d, J = 8.0 Hz, 1H, CCHNCHCC***H***), 7.78 (d, J = 8.0 Hz, 1H, CCC***H***CHCHCHCCHNC), 7.60 (t, J = 7.9 Hz, 1H, CCC***H***CHCHCHCCHNC), 7.62 (t, J = 7.9 Hz, 1H, CCCHCHC***H***CHCCHNC), 7.44 (d, J = 5.3 Hz, 1H, SC***H***CH), 7.10 (d, J = 5.3 Hz, 1H, SCHC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (CCHN***C***HCCH), 144.9 (C***C***HNCHCCH), 134.6 (S***C***CCl), 131.0 (CCCH***C***HCHCHCCHNC), 130.7 (C***C***CHCHCHCHCCHNC), 128.4 (SCH***C***H), 128.3 (CCCHCHCHCHC***C***HNC),

128.0 (S**C**HCH), 127.6 (CCCHCH**C**HCHCCHN), 126.0 (CC**C**HCHCHCHCCHN), 125.2 (CCCHCHCHCH**C**CHNC), 125.0 (CCCHCH**C**HCHCCHNC), 123.5 (SC**C**Cl). Elemental analysis: calcd (%) for $C_{13}H_8ClNS$ (245.73): C 63.54, H 3.28; found: C 63.50, H 3.09.

*3-Methyl-2-(4-nitrophenyl)-furan (**16**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.5 Hz, 2H, CHC**H**CNO$_2$), 7.69 (d, J = 8.5 Hz, 2H, C**H**CHCNO$_2$), 7.19 (s, 1H, OC**H**), 6.32 (s, 1H, OCHC**H**), 2.22 (s, 3H, CC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6 (**C**NO$_2$), 145.4 (O**C**CCH$_3$), 142.6 (O**C**HCH), 137.6 (**C**-1′ on phenyl), 124.9 (**C**HCHCNO$_2$), 124.1 (CH**C**HCNO$_2$), 120.8 (OC**C**CH$_3$), 116.1 (OCH**C**H), 12.4 (C**C**H$_3$). Elemental analysis: calcd (%) for $C_{11}H_9NO_3$ (203.19): C 65.02, H 4.46; found: C 65.11, H 4.37.

*3-Methyl-2-(1-naphthyl)furan (**17**)*

This compound was characterized by comparison with previously reported ^{1}H and ^{13}C NMR data.[17a]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.76 (m, 3H, CCCHC**H**CHC**H**CC**H**CHCH), 7.50–7.38 (m, 5H, CCC**H**CHC**H**CHCCHC**H**C**H** and OC**H**CH), 6.38 (s, 1H, OCHC**H**), 2.00 (s, 3H, CC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (Ar), 141.6 (Ar), 133.9 (Ar), 132.0 (Ar), 128.7 (Ar), 128.3 (Ar), 128.0 (Ar), 126.3 (Ar), 126.2 (Ar), 125.9 (Ar), 125.1 (Ar), 118.0 (Ar), 113.8 (OCH**C**H), 11.0 (C**C**H$_3$).

*2-(9-Anthryl)-3-methylfuran (**18**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H, anthryl), 8.04 (d, J = 8.0 Hz, 2H, anthryl), 7.74 (d, J = 8.0 Hz, 2H, anthryl), 7.66 (s, 1H, furan), 7.50–7.40 (m, 4H, anthryl), 6.57 (s, 1H, furan), 1.88 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7 (Ar), 142.3 (Ar), 131.8 (Ar), 131.3 (Ar), 128.5 (Ar), 128.4 (Ar), 126.3 (Ar), 126.1 (Ar), 126.0 (Ar), 125.2 (Ar), 120.0 (Ar), 113.2 (Ar), 10.4 (Me). Elemental analysis: calcd (%) for $C_{19}H_{14}O$ (258.31): C 88.34, H 5.46; found: C 88.57, H 5.37.

*4-(3-Methylfuran-2-yl)-pyridine (**19**)*

This compound was characterized by comparison with previously reported ^{1}H and ^{13}C NMR data.[17b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 4.8 Hz, 2H, C**H**N), 7.43 (d, J = 4.8 Hz, 2H, C**H**CHN), 7.19 (s, 1H, OC**H**), 6.30 (s, 1H, OCHC**H**), 2.28 (s, 3H, CC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0 (**C**HN), 145.9 (O**C**CCH$_3$), 142.4 (O**C**HCH), 138.5 (**C**-1′ on pyridyl), 120.8 (**C**CH$_3$), 118.7 (**C**HCHN), 115.8 (OCH**C**H), 12.2 (C**C**H$_3$).

*3-(3-Methylfuran-2-yl)-quinoline (**20**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H, C**H**N), 8.22 (s, 1H, NCHCC**H**C), 8.02 (d, J = 8.0 Hz, 1H, NCC**H**), 7.77 (d, J = 8.0 Hz, 1H, NCCC**H**CH), 7.60 (t, J = 7.9 Hz, 1H, NCCHC**H**), 7.48 (t, J = 7.9 Hz, 1H, NCCCHC**H**), 7.41 (s, 1H, OC**H**), 6.33 (s, 1H, OCHC**H**), 2.32 (s, 3H, CC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1 (**C**HN), 146.6 (O**C**CCH$_3$), 146.3 (N**C**CH), 141.9 (O**C**HCH), 130.7 (NCHC**C**H), 129.3 (NCCH**C**H), 129.2 (NC**C**HCH), 127.9 (NCC**C**H), 127.8 (NC**C**CH), 127.0 (NCCCH**C**H), 125.2 (NC**C**CH), 118.4 (**C**CH$_3$), 115.4 (OCH**C**H), 11.9 (C**C**H$_3$). Elemental analysis: calcd (%) for $C_{14}H_{11}NO$ (209.24): C 80.36, H 5.30; found: C 80.49, H 5.19.

*4-(3-Methylfuran-2-yl)-isoquinoline (**21**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H, CCHNC**H**CCHCHCHCH), 8.47 (s, 1H, CC**H**NCHCCHCHCHCH), 7.97–7.90 (m, 2H, CCHNCHCC**H**CHCHC**H**), 7.62 (t, J = 8.0 Hz, 1H, CCHNCHCCHCHC**H**CH), 7.55 (t, J = 8.0 Hz, 1H, CCHNCHCCHC**H**CHCH), 7.49 (s, 1H, OC**H**CH), 6.40 (s, 1H, OCHC**H**), 2.07 (s, 3H, C**C**H$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (CCHN**C**HCCHCHCHCH), 146.4 (O**C**CCH$_3$), 143.7 (C**C**HNCHCCHCHCHCH), 142.4 (O**C**HCH), 134.3 (**C**CHNCHCCHCHCHCH), 130.7 (CCHNCHCCHCH**C**HCH), 128.6 (CCHNCHCCHCHCHCH**C**), 127.9 (CCHNCHC**C**HCHCHCHC), 127.3 (CCHNCHCCH**C**HCHCHC), 125.3 (CCHNCHCCHCHCH**C**HC), 122.4 (CCHNCH**C**CHCHCHCHC), 119.3 (OC**C**CH$_3$), 114.1 (OCH**C**H), 11.0 (C**C**H$_3$). Elemental analysis: calcd (%) for $C_{14}H_{11}NO$ (209.24): C 80.36, H 5.30; found: C 80.27, H 5.44.

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