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Reactivity of C–H bonds of polychlorobenzenes for palladium-catalysed direct arylations with aryl bromides

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The reactivity of polychlorobenzenes *vs.* polyfluorobenzenes for palladium-catalysed direct arylation was studied. The $PdCl(C_3H_5)$(dppb)/KOAc system was found to promote the direct arylation of some polychlorobenzenes with aryl bromides. However, the reactivity of polychlorobenzenes was found to be lower than that of polyfluorobenzenes. The best yields were obtained from the coupling of 1,2,4,5-tetrachlorobenzene or 1,3,5-trichlorobenzene with electron-deficient aryl bromides. The C3 arylation of 2,5-dichlorothiophene was also found to proceed nicely.

Introduction

Among benzene derivatives, several (poly)chlorobenzene derivatives display important biological properties. For example, lamotrigine is an anticonvulsant used in the treatment of epilepsy, hexachlorophene is a disinfectant used in soaps, ambigol A also has antimicrobial activity, dicloxacillin is an antibiotic, clobuzarit is an antirheumatic, and tanomastat is a protease inhibitor (Fig. 1). Therefore, the discovery of general simple routes for access to a variety of (poly)chlorobenzene derivatives has potential in medicinal chemistry.

The direct coupling of arenes with aryl halides *via* C–H bond activation/functionalisation provides a cost-effective and environmentally attractive procedure for the preparation of biaryls.[1,2] Such couplings are very attractive compared to classical palladium-catalysed reactions such as Stille, Suzuki or Negishi couplings as they do not require the preliminary synthesis of organometallic derivatives.[3] Moreover, the major by-product is HX (X = I, Br or Cl) associated to a base instead of a metallic salt using more classical coupling procedures.

The reactivity of arenes such as polyfluorobenzenes for the palladium-catalysed direct arylation has been largely studied in recent years.[4–6] On the other hand, the influence of chloro substituents on benzenes for such couplings has attracted much less attention.[7–9] The palladium-catalyzed 2-arylation of 4-chlorobenzamide or 6-arylation of 3,4-dichlorobenzamide using aryl iodides as the coupling partners has been recently reported by Wang and co-workers (Fig. 2, top).[8b] They demonstrated that the amide group directs the arylation at the less hindered *ortho*-position of the amide. Similarly, Larrosa and co-workers described that the carboxylic acid group in 2,4-dichlorobenzoic acid allows for direct arylation at C6 (Fig. 2, bottom).[8c]

The Gibbs free energies of activation for direct arylation *via* the concerted metalation deprotonation (CMD)[10] pathway of several polychloro- and polyfluorobenzenes have been calculated by Gorelsky (Fig. 3).[10c] A lower reactivity of pentachlorobenzene compared to pentafluorobenzene could be expected as the energies of activation ($\Delta G_{298\ K}$) for the cleavage of C–H bonds are 27.2 and 21.9, respectively. Similarly, 1,3,5-trichlorobenzene was expected to be less reactive than 1,3,5-trifluorobenzene (energies: 28.5 *vs.* 24.5); and for 1,3-dichlorobenzene, the most reactive C–H should be at the C2 position. However, as these calculated reactivities have not yet been confirmed by experiments, the outcome of the reaction of polychlorobenzenes with aryl halides in the presence of palladium-catalysts was quite unpredictable and needed to be investigated.

Here, we wish to report on (i) the influence of chloro-substituents on benzene on the reactivity and regioselectivity of the palladium-catalysed direct arylation with aryl halides; (ii) the scope of the reaction using a set of aryl bromides.

Results and discussion

Commercially available pentachlorobenzene and 4-bromobenzonitrile were employed as the test substrates (Scheme 1, Table 1). We initially examined the influence of the nature of the base on the yield of this reaction using DMA as the solvent and 2 mol% of $PdCl(C_3H_5)$(dppb) as the catalyst, as such conditions were previously found operative for some direct arylations of (hetero)aromatics.[2b] In all cases, partial conversion of 4-bromobenzonitrile was observed. In the presence of NaOAc, KOAc or K_2CO_3 as bases, very similar yields of **1** were obtained, whereas CsOAc was less effective

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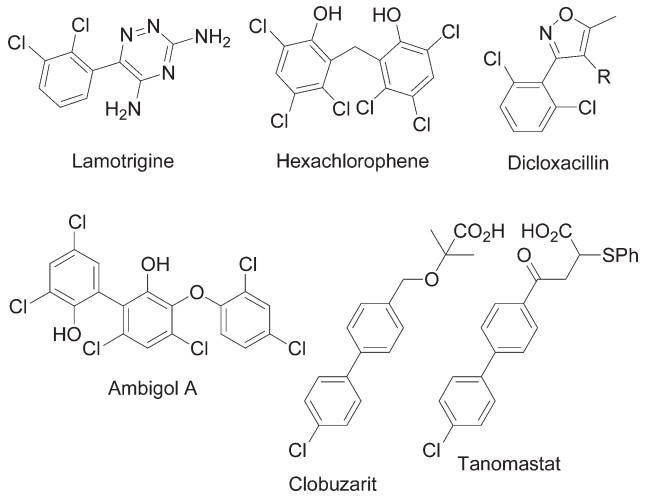


Fig. 1 Examples of bioactive (poly)chlorobenzenes.

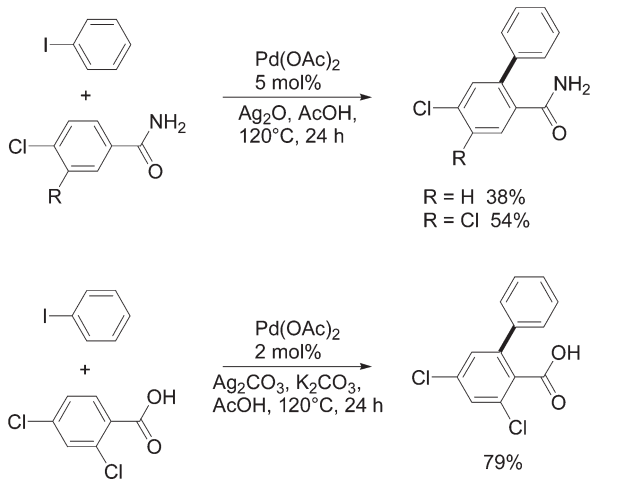


Fig. 2 Reported Pd-catalysed direct arylations of mono- and di-chlorobenzenes.[8b,c]

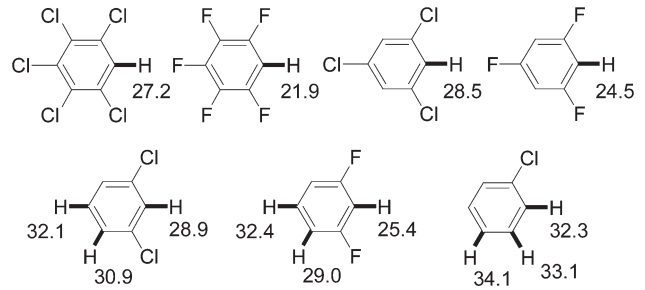
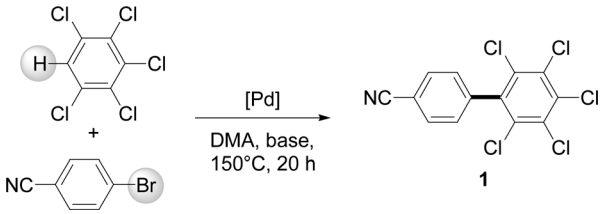


Fig. 3 Gibbs free energies of activation ($\Delta G_{298\ K}$) of the cleavage of C–H bonds for different polyhaloarenes in the CMD process using the [Pd(C_6H_5)(PMe_3)(OAc)] catalyst.[10c]

(Table 1, entries 1–4). The ratio of the reactants also appeared to have a minor influence on the yield. Another catalyst precursor was also employed. However, the use of phosphine-free $Pd(OAc)_2$ led to **1** in similar yield (Table 1, entry 6).

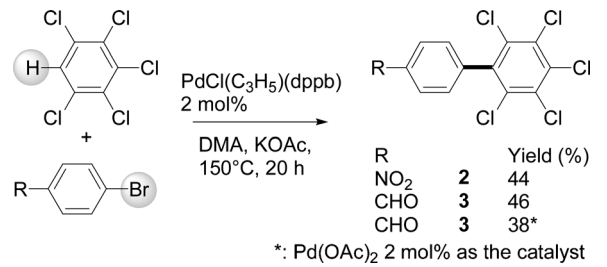


Scheme 1 Influence of the reaction conditions for the palladium-catalysed direct arylation of pentachlorobenzene with 4-bromobenzonitrile.

Table 1 Influence of the reaction conditions for the palladium-catalysed direct arylation of pentachlorobenzene with 4-bromobenzonitrile (Scheme 1)[a]

Entry	Ratio ArBr : C_6HCl_5	Catalyst (mol%)	Base	Yield in **1** (%)
1	1 : 1.5	$PdCl(C_3H_5)(dppb)$ (2)	NaOAc	23
2	1 : 1.5	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	24
3	1 : 1.5	$PdCl(C_3H_5)(dppb)$ (2)	CsOAc	8
4	1 : 1.5	$PdCl(C_3H_5)(dppb)$ (2)	K_2CO_3	21
5	1 : 3	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	25
6	1 : 1.5	$Pd(OAc)_2$ (2)	KOAc	25

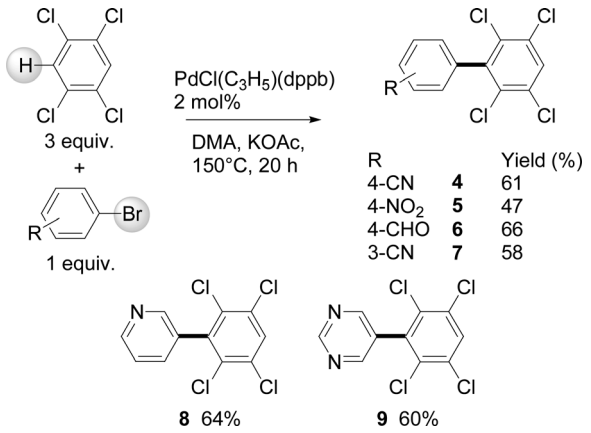
[a] Conditions: base (4 equiv.), DMA, 20 h, 150 °C.



Scheme 2 Direct arylations of pentachlorobenzene with aryl bromides.

The influence of two other bromobenzene substituents on the reactivity for the coupling with pentachlorobenzene was then examined (Scheme 2). In the presence of the electron-deficient aryl bromides, 4-bromonitrobenzene or 4-bromobenzaldehyde, the products **2** and **3** were obtained in 44% and 46% yields, respectively, when $PdCl(C_3H_5)(dppb)$ was employed as the catalyst. The use of $Pd(OAc)_2$ catalyst gave **3** in a lower yield. Again, in all cases, only a partial conversion of the aryl bromide and pentachlorobenzene was observed.

The reactivity of 1,2,4,5-tetrachlorobenzene was found to be slightly higher than that of pentachlorobenzene (Scheme 3). For these couplings, in order to avoid the formation of 1,4-diarylated tetrachlorobenzenes, 3 equiv. of 1,2,4,5-tetrachlorobenzene was employed. In the presence of aryl bromides substituted at C4 by nitrile, nitro or formyl substituents, the desired monoarylation products **4**–**6** were obtained in 47–66% yields, and no significant amount of diarylation products was formed. From 3-bromobenzonitrile, a similar yield of 58% for **7** was obtained. We also found that the coupling of 3-bromopyridine or 5-bromopyrimidine proceeded quite nicely to give **8** and **9** in 64% and 60% yields, respectively.

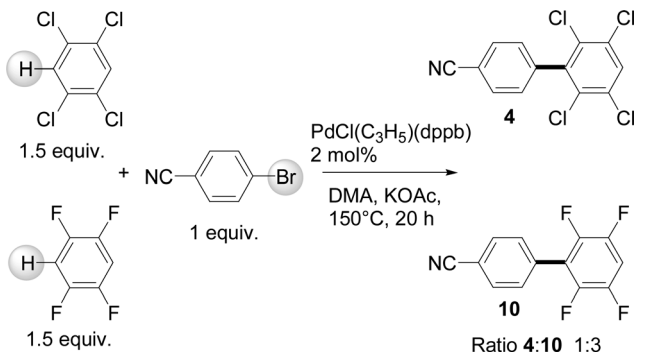


Scheme 3 Direct arylation of 1,2,4,5-tetrachlorobenzene with various aryl bromides.

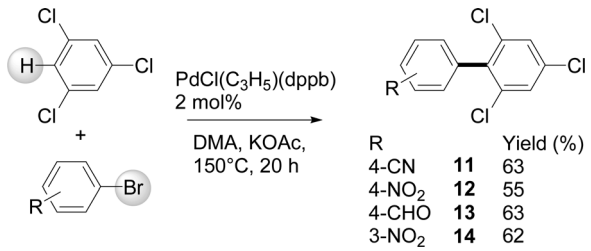
In order to gain more insight on the reactivity of chloro- *vs.* fluoro-substituted benzenes, we compared the reactivity of tetrachloro- and tetrafluorobenzenes. An equimolar mixture of 1,2,4,5-tetrachlorobenzene and 1,2,4,5-tetrafluorobenzene reacted with 4-bromobenzonitrile gave a mixture of products **4** and **10** in a 1 : 3 ratio (Scheme 4). Moreover, some formation of the diarylation product of 1,2,4,5-tetrafluorobenzene was also detected using GC/MS analysis, whereas no diarylation of 1,2,4,5-tetrachlorobenzene was observed. This result confirms that 1,2,4,5-tetrachlorobenzene is less reactive than 1,2,4,5-tetrafluorobenzene for Pd-catalysed direct arylation.

Gorelsky had calculated a Gibbs free energy of activation for direct arylation of 1,3,5-trichlorobenzene of 28.5 (Fig. 3).[10c] Under similar conditions, the desired arylation products **11**–**14** were obtained in higher yields with 1,3,5-trichlorobenzene than with pentachlorobenzene (Scheme 5). Very similar yields were obtained from cyano-, nitro- or formyl-substituted bromobenzenes.

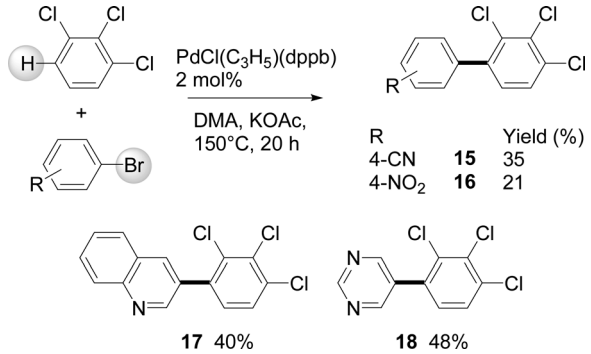
1,2,3-Trichlorobenzene reacted with 4-bromobenzonitrile, 4-bromonitrobenzene or 4-bromobenzaldehyde to give **15** and **16** in poor yields (Scheme 6). However, the reaction was regioselective in favour of the formation of the 4-arylated products. Better yields were obtained for the coupling with 3-bromoquinoline and 5-bromopyrimidine, as the desired products **17** and **18** were obtained in 40% and 48% yields, respectively.



Scheme 4 Competitive experiment for palladium-catalysed direct arylation using an equimolar mixture of 1,2,4,5-tetrachlorobenzene and 1,2,4,5-tetrafluorobenzene.



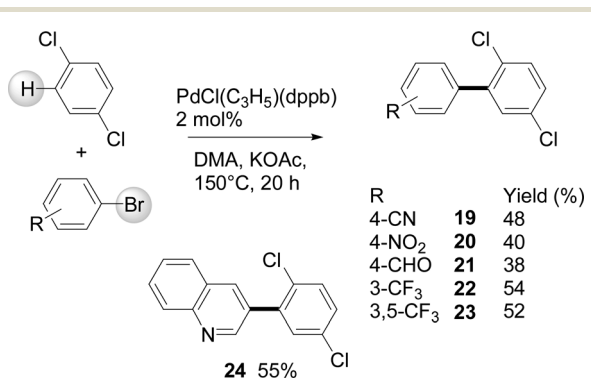
Scheme 5 Direct arylation of 1,3,5-trichlorobenzene with various aryl bromides.



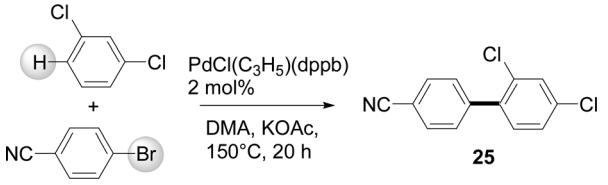
Scheme 6 Direct arylation of 1,2,3-trichlorobenzene with various aryl bromides.

Unexpectedly, quite good yields were obtained for the coupling of 1,4-dichlorobenzene with aryl bromides. From 4-bromobenzonitrile, **19** was obtained in 48% yield (Scheme 7). Both 3-trifluoromethylbromobenzene and 3,5-bis(trifluoromethyl)bromobenzene also gave the expected products **22** and **23** in quite good yields. The best yield was obtained in the presence of 3-bromoquinoline to give **24** in 55% yield.

According to Gorelsky, for 1,3-dichlorobenzene, carbon 2 should be more reactive than carbon 4 (energies: 28.9 *vs.* 30.9) (Fig. 3).[10c] Our first attempt of coupling 1,3-dichlorobenzene with 4-bromobenzonitrile using $PdCl(C_3H_5)$(dppb) as catalyst and KOAc as base in DMA led to a mixture of two regioisomers according to GC/MS analysis. Surprisingly,



Scheme 7 Direct arylation of 1,4-dichlorobenzene with various aryl bromides.



Scheme 8 Direct arylation of 1,3-dichlorobenzene with 4-bromobenzonitrile.

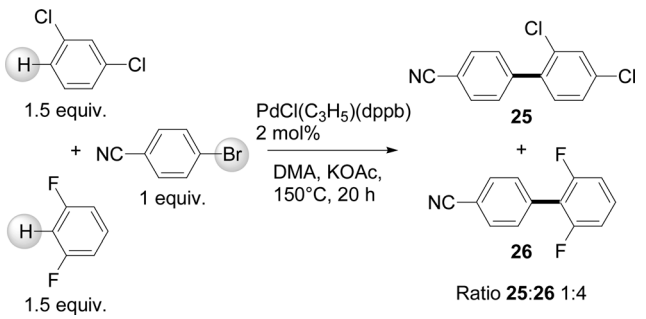
Table 2 Influence of the reaction conditions for the palladium-catalysed direct arylation of 1,3-dichlorobenzene with 4-bromobenzonitrile (Scheme 8)[a]

Entry	Catalyst (mol%)	Solvent	Conv. (%)	Yield in 25 (%)
1	$PdCl(C_3H_5)(dppb)$ (2)	DMA	57	34
2	$PdCl(C_3H_5)(dppb)$ (2)	DMF	64	25
3	$PdCl(C_3H_5)(dppb)$ (2)	NMP	56	26
4	$Pd(OAc)_2$ (2)	DMA	47	—
5	$Pd(OAc)_2$ (2)/dppe (2)	DMA	69	33
6	$Pd(OAc)_2$ (2)/dppb (2)	DMA	54	—

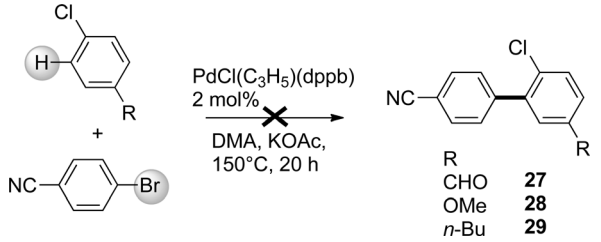
[a] Conditions: 4-bromobenzonitrile (1 equiv.), 1,3-dichlorobenzene (3 equiv.), KOAc (4 equiv.), 20 h, 150 °C, conv. of 4-bromobenzonitrile; in all cases, **25** was obtained in 66% regioselectivity.

the major product of the reaction was the C4-arylated 1,3-dichlorobenzene **25** with a selectivity of 66% (Scheme 8, Table 2). Arylation at the less reactive C4 position might be due to the steric hindrance of the chloro substituents. The influence of several reaction conditions has been studied, but in all cases, the same regioselectivity was obtained. However, the reactions performed in DMF or NMP led to lower yields of **25** due to the formation of side-products, whereas $Pd(OAc)_2$ gave a lower conversion.

The reaction of an equimolar mixture of 1,3-dichlorobenzene and 1,3-difluorobenzene using the same reaction conditions gave a mixture of the 2-arylated 1,3-difluorobenzene **26** and the 4-arylated 1,3-dichlorobenzene **25** in a 4 : 1 ratio (Scheme 9). Again, the fluorobenzene derivative is more reactive than the chlorobenzene derivative. Moreover, the regioselectivities of these two reactions were different, with the less sterically demanding fluoro substituents making the calculated arylation at C2 possible (Fig. 3).

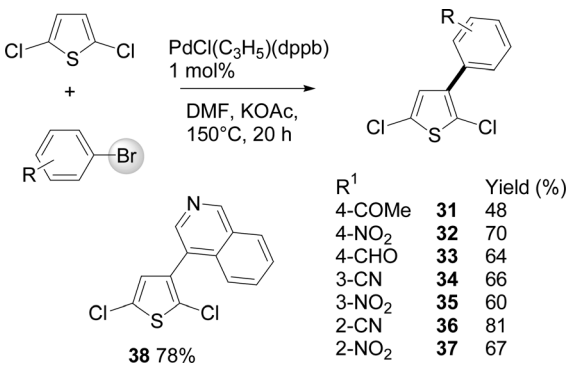


Scheme 9 Competitive experiment for palladium-catalysed direct arylation using an equimolar mixture of 1,3-dichlorobenzene and 1,3-difluorobenzene.



Scheme 10 Attempts of direct arylation of 4-substituted chlorobenzenes with 4-bromobenzonitrile.

Scheme 11 Direct arylation of 2,5-dichlorothiophene with various aryl bromides.



Scheme 12 Direct arylation of 2,5-dichlorothiophene with various aryl bromides.

The reactivity of three 4-substituted chlorobenzenes with 4-bromobenzonitrile as coupling partner using similar reaction conditions was also examined (Scheme 10). However, the presence of electron-withdrawing or electron-donating substituents on chlorobenzene led to unreacted aryl bromide, and no formation of the target products **27**–**29** was detected.

Finally, we examined the reactivity of 2,5-dichlorothiophene for direct arylation (Schemes 11 and 12). The influence of a few reaction conditions has been examined. The best yield in **30** was obtained using 1 mol% $PdCl(C_3H_5)(dppb)$ as catalyst in DMF and KOAc as base. However, quite similar results were obtained in DMA or using 2 mol% $Pd(OAc)_2$/dppb as catalyst (Table 3).

The reaction tolerates a variety of substituents on the aryl bromide such as acetyl, formyl, nitrile or nitro (Scheme 12). The best yields were obtained from the reactions with 2-bromobenzonitrile and 4-bromoisoquinoline. With these reactants, the desired products **36** and **38** were obtained in 81 and 78% yields, respectively. On the other hand, from 4-bromoacetophenone, **31** was only produced in 48% yield due to the formation of unidentified side-products.

Table 3 Influence of the reaction conditions for the palladium-catalysed direct arylation of 2,5-dichlorothiophene with 4-bromobenzonitrile (Scheme 11)[a]

Entry	Catalyst (mol%)	Base	Solvent	Conv. (%)	Yield in **30** (%)
1	$PdCl(C_3H_5)(dppb)$ (1)	KOAc	DMA	70	56
2	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	DMA	78	60
3	$PdCl(C_3H_5)(dppb)$ (1)	CsOAc	DMA	30	—
4	$PdCl(C_3H_5)(dppb)$ (1)	KOAc	NMP	60	50
5	$PdCl(C_3H_5)(dppb)$ (1)	KOAc	DMF	87	63
6	$PdCl(C_3H_5)(dppb)$ (0.5)	KOAc	DMF	44	—
7	$Pd(OAc)_2$ (2)/dppb (2)	KOAc	DMF	88	62

[a] Conditions: 4-bromobenzonitrile (1 equiv.), 2,5-dichlorothiophene (2 equiv.), base (4 equiv.), 20 h, 150 °C, conv. of 4-bromobenzonitrile.

Conclusions

In summary, we report herein the first examples of palladium-catalysed direct *ortho*-arylations of polychlorobenzene derivatives with aryl bromides using chloro-substituent as a directing group. The reactivity of polychlorobenzenes was found to be lower than that of the corresponding polyfluorobenzene derivatives as calculated by Gorelsky. The influence of the number and positions of chloro-substituents on benzene on their reactivity was studied. The steric properties of chloro-substituents likely partially modify the reactivity of this family of compounds. Although moderate yields were obtained in several cases, this method gives access to functionalised polychlorobiphenyls in only one step.

Experimental

General remarks

All reactions were performed in Schlenk tubes under argon. DMA analytical grade was not distilled before use. Potassium acetate 99+ was used. Commercial aryl halide derivatives were used without purification. ^1H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (^1H: 7.26 and ^{13}C: 77.0). Flash chromatography was performed on silica gel (230–400 mesh).

Preparation of the $PdCl(C_3H_5)(dppb)$ catalyst[11]

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 was added, and 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 (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for the synthesis of compounds 1–31

As a typical experiment, the reaction of the aryl bromide (1 mmol), polychlorobenzene derivative (1.5 or 3 mmol) and KOAc (0.392 g, 4 mmol) at 150 °C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

2′,3′,4′,5′,6′-Pentachlorobiphenyl-4-carbonitrile (1)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **1** was obtained in 25% (0.088 g) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 138.4, 134.2, 132.6, 132.4, 132.2, 130.0, 118.2, 113.0. Elemental analysis: calcd (%) for $C_{13}H_4Cl_5N$ (351.44): C 44.43, H 1.15; found: C 44.50, H 1.22.

2,3,4,5,6-Pentachloro-4′-nitrobiphenyl (2)[12]

From 4-bromonitrobenzene (0.202 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **2** was obtained in 44% (0.163 g) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H).

2′,3′,4′,5′,6′-Pentachlorobiphenyl-4-carbaldehyde (3)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **3** was obtained in 46% (0.163 g) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 142.8, 139.1, 136.4, 133.9, 132.3, 132.2, 130.0, 129.8. Elemental analysis: calcd (%) for $C_{13}H_5Cl_5O$ (354.44): C 44.05, H 1.42; found: C 44.14, H 1.60.

2′,3′,5′,6′-Tetrachlorobiphenyl-4-carbonitrile (4)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **4** was obtained in 61% (0.193 g) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.62 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 140.7, 132.5, 132.4, 131.4, 130.9, 130.0, 118.3, 112.8. Elemental analysis: calcd (%) for $C_{13}H_5Cl_4N$ (317.00): C 49.26, H 1.59; found: C 49.40, H 1.49.

2,3,5,6-Tetrachloro-4′-nitrobiphenyl (5)

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **5** was obtained in 47% (0.158 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 8.9 Hz, 2H), 7.64 (s, 1H), 7.43 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 143.4, 140.4, 132.5, 131.4, 131.0, 130.3, 124.0. Elemental analysis: calcd (%) for $C_{12}H_5Cl_4NO_2$ (336.98): C 42.77, H 1.50; found: C 42.64, H 1.38.

2′,3′,5′,6′-Tetrachlorobiphenyl-4-carbaldehyde (6)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **6** was obtained in 66% (0.211 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 143.0, 141.3, 136.3, 132.3, 131.5, 130.7, 130.0, 129.9. Elemental analysis: calcd (%) for $C_{13}H_6Cl_4O$ (320.00): C 48.79, H 1.89; found: C 48.62, H 2.04.

2′,3′,5′,6′-Tetrachlorobiphenyl-3-carbonitrile (7)

From 3-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **7** was obtained in 58% (0.184 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 138.3, 133.6, 132.7, 132.4, 132.3, 131.8, 130.9, 129.6, 118.2, 113.2. Elemental analysis: calcd (%) for $C_{13}H_5Cl_4N$ (317.00): C 49.26, H 1.59; found: C 49.21, H 1.64.

3-(2,3,5,6-Tetrachlorophenyl)-pyridine (8)

From 3-bromopyridine (0.158 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **8** was obtained in 64% (0.187 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (bs, 1H), 8.47 (bs, 1H), 7.64 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.4, 138.5, 138.1, 132.5, 132.2, 131.2. Elemental analysis: calcd (%) for $C_{11}H_5Cl_4N$ (292.97): C 45.10, H 1.72; found: C 45.27, H 1.89.

5-(2,3,5,6-Tetrachlorophenyl)-pyrimidine (9)

From 5-bromopyrimidine (0.159 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **9** was obtained in 60% (0.176 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.61 (s, 2H), 7.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 157.0, 135.7, 132.7, 132.2, 131.7, 131.6. Elemental analysis: calcd (%) for $C_{10}H_4Cl_4N_2$ (293.96): C 40.86, H 1.37; found: C 40.77, H 1.27.

2′,4′,6′-Trichlorobiphenyl-4-carbonitrile (11)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **11** was obtained in 63% (0.178 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.1 Hz, 2H), 7.39 (s, 2H), 7.30 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 136.3, 135.0, 134.9, 132.2, 130.6, 128.3, 118.5, 112.5. Elemental analysis: calcd (%) for $C_{13}H_6Cl_3N$ (282.55): C 55.26, H 2.14; found: C 55.11, H 2.07.

2,4,6-Trichloro-4′-nitrobiphenyl (12)

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **12** was obtained in 55% (0.166 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.7 Hz, 2H), 7.39 (s, 2H), 7.36 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 141.3, 135.0, 134.1, 133.9, 129.9, 127.4, 122.7. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.80, H 1.88.

2′,4′,6′-Trichlorobiphenyl-4-carbaldehyde (13)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **13** was obtained in 63% (0.180 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.39 (s, 2H), 7.35 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 142.0, 136.9, 136.1, 135.0, 134.7, 130.5, 129.7, 128.3. Elemental analysis: calcd (%) for $C_{13}H_7Cl_3O$ (285.55): C 54.68, H 2.47; found: C 54.49, H 2.67.

2,4,6-Trichloro-3′-nitrobiphenyl (14)

From 3-bromonitrobenzene (0.202 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **14** was obtained in 62% (0.187 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.7 Hz, 1H), 8.08 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.41 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 137.3, 135.9, 135.7, 135.3, 135.2, 129.5, 128.4, 125.0, 123.5. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.61, H 1.97.

2′,3′,4′-Trichlorobiphenyl-4-carbonitrile (15)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **15** was obtained in 35% (0.099 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 139.1, 134.4, 132.8, 132.6, 132.1, 130.1, 128.8, 128.5, 118.4, 112.2. Elemental analysis: calcd (%) for $C_{13}H_6Cl_3N$ (282.55): C 55.26, H 2.14; found: C 55.08, H 2.22.

2,3,4-Trichloro-4′-nitrobiphenyl (16)

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **16** was obtained in 21% (0.063 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.9, 138.8, 134.6, 132.9, 132.6, 130.3, 128.8, 128.5, 123.6. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.49, H 1.89.

3-(2,3,4-Trichlorophenyl)-quinoline (17)

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **17** was obtained in 40% (0.123 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.15–8.10 (m, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 146.9, 137.4, 136.5, 134.3, 133.3, 132.8, 131.7, 130.5, 129.4, 129.0, 128.6, 128.1, 127.5, 127.4. Elemental analysis: calcd (%) for $C_{15}H_8Cl_3N$ (308.59): C 58.38, H 2.61; found: C 58.28, H 2.57.

5-(2,3,4-Trichlorophenyl)-pyrimidine (18)

From 5-bromopyrimidine (0.159 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **18** was obtained in 48% (0.124 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.76 (s, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 156.7, 135.2, 133.9, 133.2, 128.9, 128.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_3N_2$ (259.52): C 46.28, H 1.94; found: C 46.41, H 2.01.

2′,5′-Dichlorobiphenyl-4-carbonitrile (19)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **19** was obtained in 48% (0.119 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.28–7.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.0, 133.0, 132.0, 131.4, 130.8, 130.6, 130.1, 129.6, 118.5, 112.1. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2N$ (248.11): C 62.93, H 2.84; found: C 62.74, H 2.71.

2,5-Dichloro-4′-nitrobiphenyl (20)[13]

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **20** was obtained in 40% (0.107 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.30–7.23 (m, 2H).

2′,5′-Dichlorobiphenyl-4-carbaldehyde (21)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **21** was obtained in 38% (0.095 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 9.0, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 144.1, 140.7, 135.8, 132.9, 131.3, 130.9, 130.7, 130.1, 129.6, 129.3. Elemental analysis: calcd (%) for $C_{13}H_8Cl_2O$ (251.11): C 62.18, H 3.21; found: C 62.10, H 3.08.

2,5-Dichloro-3′-trifluoromethylbiphenyl (22)

From 3-trifluoromethylbromobenzene (0.225 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **22** was obtained in 54% (0.157 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 9.0, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.8, 132.9, 132.7, 133.2, 131.0, 130.8 (q, J = 32.0 Hz), 129.2, 128.7, 128.5, 126.1 (q, J = 3.9 Hz), 124.9 (q, J = 3.7 Hz), 124.0 (q, J = 271.9 Hz). Elemental analysis: calcd (%) for $C_{13}H_7Cl_2F_3$ (291.10): C 53.64, H 2.42; found: C 53.82, H 2.28.

2,5-Dichloro-3′,5′-bis-trifluoromethylbiphenyl (23)

From 1-bromo-3,5-bis(trifluoromethyl)benzene (0.293 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **23** was obtained in 52% (0.187 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.82 (s, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.32–7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 138.8, 133.2, 131.7 (q, J = 33.0 Hz), 131.4, 130.9, 130.7, 130.0, 129.6 (m), 123.1 (q, J = 271.5 Hz), 122.0 (q, J = 3.8 Hz). Elemental analysis: calcd (%) for $C_{14}H_6Cl_2F_6$ (359.09): C 46.83, H 1.68; found: C 46.74, H 1.79.

3-(2,5-Dichlorophenyl)-quinoline (24)

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **24** was obtained in 55% (0.151 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 7.9 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 9.0, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 145.7, 137.8, 137.6, 133.2, 131.5, 131.4, 131.3, 131.2, 131.0, 129.8, 128.2, 128.1, 127.8, 127.6. Elemental analysis: calcd (%) for $C_{15}H_9Cl_2N$ (274.14): C 65.72, H 3.31; found: C 65.67, H 3.17.

2′,4′-Dichlorobiphenyl-4-carbonitrile (25)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,3-dichlorobenzene (0.441 g, 3 mmol), **25** was obtained in 34% (0.084 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 1.9 Hz, 1H), 7.28 (dd, J = 8.3, 1.9 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 137.2, 135.0, 133.0, 132.0, 131.7, 130.2, 130.1, 127.5, 118.6, 111.9. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2N$ (248.11): C 62.93, H 2.84; found: C 63.07, H 3.04.

4-(2,5-Dichlorothiophen-3-yl)-benzonitrile (30)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **30** was obtained in 63% (0.160 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 6.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 136.2, 132.4, 129.0, 127.4, 126.8, 123.6, 118.5, 111.7. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.12, H 2.14.

1-[4-(2,5-Dichlorothiophen-3-yl)-phenyl]-ethanone (31)

From 4-bromoacetophenone (0.199 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **31** was obtained in 48% (0.130 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 6.94 (s, 1H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 137.8, 137.0, 136.3, 128.6, 128.5, 127.1, 127.0, 123.0, 26.6. Elemental analysis: calcd (%) for $C_{12}H_8Cl_2OS$ (271.16): C 53.15, H 2.97; found: C 53.29, H 3.09.

2,5-Dichloro-3-(4-nitrophenyl)-thiophene (32)

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **32** was obtained in 70% (0.192 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 6.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 139.5, 135.8, 129.2, 127.6, 126.8, 123.9, 123.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 43.98, H 1.89.

4-(2,5-Dichlorothiophen-3-yl)-benzaldehyde (33)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **33** was obtained in 64% (0.164 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 139.1, 136.8, 135.5, 129.9, 128.9, 127.2, 127.0, 123.3. Elemental analysis: calcd (%) for $C_{11}H_6Cl_2OS$ (257.14): C 51.38, H 2.35; found: C 51.09, H 2.20.

3-(2,5-Dichlorothiophen-3-yl)-benzonitrile (34)

From 3-bromobenzonitrile (0.182 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **34** was obtained in 66% (0.168 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.5, 132.6, 131.8, 131.4, 129.5, 127.4, 126.8, 123.2, 118.4, 112.9. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.20, H 2.17.

2,5-Dichloro-3-(3-nitrophenyl)-thiophene (35)

From 3-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **35** was obtained in 60% (0.164 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 135.6, 134.8, 134.2, 129.6, 127.5, 126.8, 123.5, 123.3, 122.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 43.67, H 1.70.

2-(2,5-Dichlorothiophen-3-yl)-benzonitrile (36)

From 2-bromobenzonitrile (0.182 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **36** was obtained in 81% (0.205 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 6.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 134.9, 133.4, 132.7, 130.7, 128.7, 127.2, 127.1, 125.0, 117.6, 112.5. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.07, H 1.84.

2,5-Dichloro-3-(2-nitrophenyl)-thiophene (37)

From 2-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **37** was obtained in 67% (0.183 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 6.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 134.1, 132.9, 132.3, 129.5, 128.2, 127.0, 126.8, 124.7, 123.9. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 44.03, H 1.97.

4-(2,5-Dichlorothiophen-3-yl)-isoquinoline (38)

From 4-bromoisoquinoline (0.208 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **38** was obtained in 78% (0.218 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.49 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.75–7.60 (m, 3H), 6.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 143.8, 134.1, 134.0, 130.9, 128.4, 128.1, 127.5, 127.0, 125.1, 124.9, 124.4. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2NS$ (280.17): C 55.73, H 2.52; found: C 55.49, H 2.31.

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