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Palladium-catalyzed arylation of ferrocene derivatives: a convenient high yield route to 1,1′-bis(halophenyl)ferrocenes

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Abstract

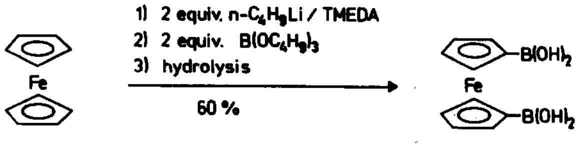
The Pd-catalyzed cross-coupling reaction between halobenzenes and ferrocene-1,1′-diboronic acid is reported. Condensation proceeds smoothly to give 1,1′-diphenyl- and 1,1′-bis(halophenyl)-substituted ferrocenes bearing fluoro, chloro and bromo substituents in good yields. An effective synthesis of the intermediate ferrocene-1,1′-diboronic acid is described.

1. Introduction

Following the initial reports [1,2], the Pd-catalyzed cross-coupling of bromoaromatics and arylboronic acid derivatives has developed into a powerful method for carbon–carbon bond formation [3,4]. However, in the case of condensations involving pyrrole, thiophene or ferrocene derivatives as starting materials, only poor results are generally obtained, loss of the boronic functionality being observed instead of carbon–carbon bond formation [3b]. On the other hand, the regiospecificity and the high tolerance towards functional groups make this coupling reaction very attractive for the synthesis of molecules containing electron-rich aromatics. Thus, we thought it of interest to develop an efficient procedure for use of Pd-catalyzed condensation to give 1,1′-bis(halophenyl)ferrocenes. Because of the reactivity of the carbon–halogen bond in the phenyl groups, such compounds are important starting materials for the synthesis of many ferrocene compounds in organic and polymer chemistry. When used as monomers they could even give polymers such as poly(1,1′-ferrocenearylene)s, potentially interesting materials in respect of their electrical and nonlinear optical properties [5].

2. Results and discussion

Ferrocene-1,1′-diboronic acid (2) was judged to be a suitable starting material for the Pd-catalyzed synthesis of the desired 1,1′-bis(halophenyl)ferrocenes. Ferrocene-1,1′-diboronic acid (2) has been obtained in the past only in 25% yield as a by-product in the synthesis of ferroceneboronic acid [6]. However, when equimolar amounts of n-butyllithium and TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylene diamine) are used in the initial lithiation step, the yield of the 1,1′-dilithioferrocene reagent is substantially increased. Subsequent reaction of this reagent with tributylborate followed by hydrolysis yielded compound **2** in 60% yield (eqn. (1)). Its purity was checked by TLC, ^1H and ^{13}C NMR spectroscopy, and found to exceed 98%.



1 2 (1)

In order to optimize the reaction conditions for the Pd-catalyzed condensation, 1,1′-diphenylferrocene (**7a**) was synthesized as a model compound by the route shown in eqns. (2) and (3), with various reaction media and catalysts. Subsequently, 1 mol% of Pd catalyst per

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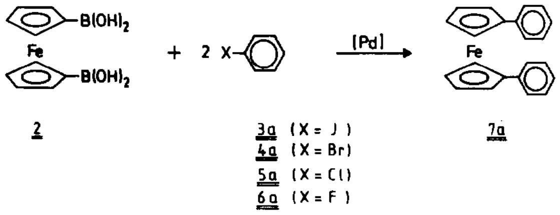
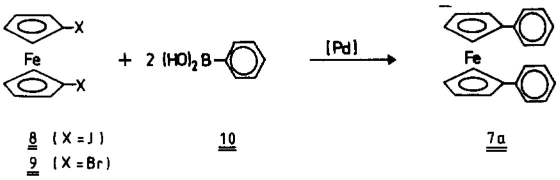
coupling step was always used because it was found that use of higher concentrations of catalyst had no effect on the yields, whereas the use of smaller quantities resulted in a lower yield.



(2)



(3)

The reactions were monitored by analyzing samples of the product mixtures at regular intervals (TLC and NMR). The studied yields of compound **7a** were based on the integrals of the ^{1}H NMR resonances of the ferrocenylene protons in spectra of the product mixtures. The signals from the ferrocenylene protons of product **7a** (δ 4.19 and 4.45 ppm) were well separated from those of the starting materials and from those of by-products, such as phenylferrocene (δ 4.04, 4.31 and 4.64 ppm) and ferrocene (δ 4.16 ppm), formed by hydrolysis during the conversions. The yields of **7a** were calculated from the quantity of the product mixture obtained and its composition.

Use of the system toluene/2 M aqueous Na_2CO_3/$Pd(PPh_3)_4$ (system A, Table 1) (which was successful in the coupling of benzene derivatives [3,4]) gave rather poor results. Only in the condensation of benzeneboronic acid (**10**) and 1,1'-diiodoferrocene (**8**), was a moderate yield (55%) of diphenylferrocene (**7a**) obtained (entry 4). Coupling of ferrocene-1,1'-diboronic acid (**2**) and iodobenzene (**3a**) (entry 2) gave only a 25% yield of **7a**. Yields of **7a** from bromobenzene (**4a**) (entry 1) and 1,1'-dibromoferrocene (**9**) (entry 3), respectively, were very low. In these cases, the halogen compounds were recovered almost unchanged, but the boronic acid derivatives had decomposed.

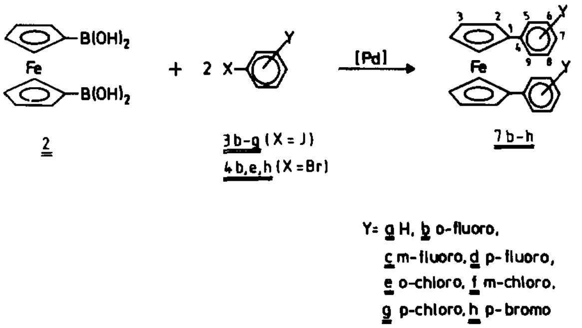
In subsequent experiments, use of other solvent/base/catalyst combinations such as DMF/NEt_3/$PdCl_2$(dppf), Et_2O/NaOH/$PdCl_2$(dppf), THF/NaOH/$PdCl_2$(dppf) and dimethoxyethane (DME)/3 M aqueous NaOH/$PdCl_2$(dppf) was examined in some detail (dppf = 1,1'-bis(diphenylphosphino)ferrocene). The system DME/3 M aqueous NaOH/$PdCl_2$(dppf) (system B, Table 1) proved to be better than all the other systems we have tested so far. In this case, **7a** was formed in 90% yield from the reaction of 1,1'-diiodoferrocene (**8**) with benzeneboronic acid (**10**) (entry 10). An identical yield was obtained from the coupling of ferrocene-1,1'-diboronic acid (**2**) and iodobenzene (**3a**) (entry 5). As expected, lower conversions were obtained from bromo-derivatives (entries 6,9). Chlorobenzene (**5a**) and fluorobenzene (**6a**) showed almost no reaction with **2** under the conditions of system B (entries 7,8).

TABLE 1. Pd-catalyzed synthesis of 1,1'-diphenylferrocene

Entry no.	Boronic acid g (mmol)	Halo-compound g (mmol)	System [a]	Conversion to **7a** (%) [b]
1	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Bromo-benzene (**4a**) 0.63 (4.0)	A	10
2	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Iodo-benzene (**3a**) 0.82 (4.0)	A	25
3	Benzene-boronic acid (**10**) 0.49 (4.0)	Dibromo-ferrocene (**9**) 0.69 (2.0)	A	Traces
4	Benzene-boronic acid (**10**) 0.49 (4.0)	Diiodo-ferrocene (**8**) 0.87 (2.0)	A	55
5	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Iodo-benzene (**3a**) 0.82 (4.0)	B	90
6	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Bromo-benzene (**4a**) 0.63 (4.0)	B	60
7	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Chloro-benzene (**5a**) 0.45 (4.0)	B	Traces
8	Ferrocene-diboronic acid (**2**) 0.55 (2.0)	Fluoro-benzene (**6a**) 0.38 (4.0)	B	Traces
9	Benzene-boronic acid (**10**) 0.49 (4.0)	Dibromo-ferrocene (**9**) 0.69 (2.0)	B	10
10	Benzene-boronic acid (**10**) 0.49 (4.0)	Diiodo-ferrocene (**8**) 0.87 (2.0)	B	90

[a] System A: toluene/2 M aqueous Na_2CO_3/$Pd(PPh_3)_4$; system B: DME/3 M NaOH/$PdCl_2$(dppf). [b] Calculated from representative ^{1}H NMR spectra of the raw product mixture.

In the light of these results, system B was judged to be a satisfactory reaction medium and was chosen for the synthesis of the desired 1,1'-bis(halophenyl)ferrocenes **7b–h**. As starting materials, ferrocene-1,1'-diboronic acid (**2**) and (usually) iodobenzene derivatives (**3b–h**) bearing an additional halogen group were used (eqn. (4)). In principle, 1,1'-diiodoferrocene (**8**) and halogen-bearing benzeneboronic acid derivatives should also be suitable starting materials. The commercial availability of compounds **3b–g** and **4b–h** favoured the route shown in eqn. (4).



(4)

In all cases the diarylated products were formed in 70–90% yields (NMR). As in the model reactions, the monoarylated ferrocene derivatives (< 10%) and ferrocene (< 2%) were formed as by-products. Figure 1 shows the relevant segments of a representative ^{1}H NMR spectrum of the product mixture obtained in the condensation shown as entry 14.

The spectrum is dominated by the resonances of the 1,1′-bis(*o*-chlorophenyl)ferrocene (**7e**). Only traces of *o*-chlorophenylferrocene (▼) and ferrocene (□) were detected. Additional small signals in the aromatic region (δ 6.8–7.8 ppm) were assigned to *o*-chloroiodobenzene (▽) and to the solvent chloroform (○). Further small peaks between δ 6.8 and 7.8 ppm were assigned to catalyst residues and other by-products, which were not identified.

Finally, *o*-fluorobromobenzene (**4b**), *o*-chlorobromobenzene (**4e**) and *p*-dibromobenzene (**4h**) were reacted with ferrocene-1,1′-diboronic acid (**2**) in order to study the activating effect of the additional halogen substituent on the reactivity of the Br–C bond. The best results were obtained with chlorobromobenzene (**4e**) (entry 18) leading to **7e** to about 90%. A comparable result was obtained with *o*-fluorobromobenzene (**4b**), 70% of **7e** being formed (entry 17). For the synthesis of 1,1′-bis(*p*-bromophenyl)ferrocene (**7h**) (entry 19), six equivalents of *p*-dibromobenzene (**4h**) had to be used in order to suppress oligomerization processes. Compound **7h** was formed in 70% yield (NMR). It can be seen that in all cases, much higher conversions were found with the substituted bromo-derivatives **4b**, **4e** and **4h** than from bromobenzene (**4a**) itself. Evidently, the additional halogen activates the C–Br bond.

The 1,1′-bis(halophenyl)ferrocenes (**7b–h**) were readily isolated from the by-products by column chromatography and crystallization from petroleum ether (for isolated yields, see: Table 2). The structures assigned to products **7b–h** were based on their ^{1}H and ^{13}C NMR spectra. These data and the melting points are given in Table 2.

In conclusion, we have described a convenient, high yield route to structurally well defined 1,1′-bis(halophenyl)ferrocenes. The method is a valuable addition to the classical routes such as reactions of ferrocene with the corresponding diazotized aniline derivatives [9,10,11a,12], treating of FeCl$_2$ with arylated cyclopentadienyl sodium [13] or transition metal catalyzed condensation of dilithioferrocene and iodoaromatics [13a]. Use of the compounds prepared in this work in the synthesis of new polymers is under investigation.

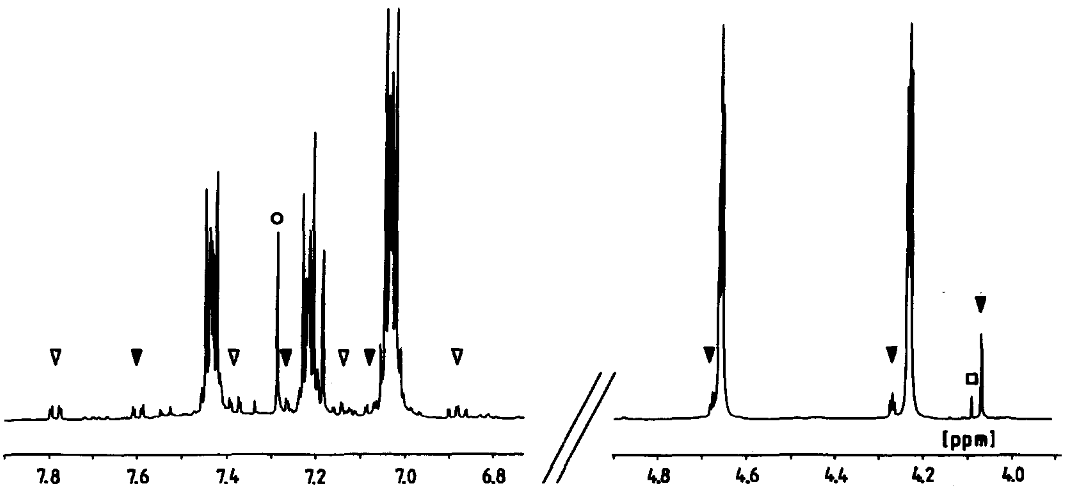


Fig. 1. Aromatic proton region of the ^{1}H NMR spectrum of 1,1′-bis(*o*-chlorophenyl)ferrocene (7e), recorded at 400 MHz in CDCl$_3$ at room temperature.

TABLE 2. Pd-catalyzed synthesis of 1,1'-bis(halophenyl)ferrocenes

Entry no.	Halobenzene g (mmol)	Diboronic acid g (mmol)	Conversion to (%) [a]	Isolated yield (%)	m.p. (°C) found/lit.	^{1}H NMR (CDCl$_3$)	^{13}C NMR (CDCl$_3$)
11	**3b** 0.89 (4.0)	**2** 0.55 (2.0)	**7b** (75) (*o*-fluoro)	55	88/– [7]	4.24 (m, 4H, H^3); 4.65 (m, 4H, H^2); 6.89, 7.09, 7.27 (3m, 8H, H^6, H^7, H^8, H^9)	69.20, 70.57 (2dd, C^2, C^3); 80.74 (s, C^1); 115.76, 123.76, 126.94, 128.61 (4dd, C^6, C^7, C^8, C^9); 125.15 (d, C^4); 159.75 (d, C^5)
12	**3c** 0.89 (4.0)	**2** 0.55 (2.0)	**7c** (70) (*m*-fluoro)	45	144/147 [8]	4.25 (m, 4H, H^3); 4.47 (m, 4H, H^2); 6.85, 7.01, 7.13 (3 m, 8H, H^5, H^7, H^8, H^9)	67.84, 70.65 (2d, C^2, C^3); 84.84 (s, C^1); 112.45, 112.66, 121.33, 129.64 (4dd, C^5, C^7, C^8, C^9); 140.04 (d, C^4); 162.92 (d, C^6)
13	**3d** 0.89 (4.0)	**2** 0.55 (2.0)	**7d** (70) (*p*-fluoro)	45	169/172 [8]	4.22 (m, 4H, H^3), 4.42 (m, 4H, H^2); 6.87, 7.18 (2m, 8H, H^5, H^6, H^8, H^9)	67.66, 70.24 (2d, C^2, C^3); 85.53 (s, C^1); 115.12, 127.20 (2dd, C^5, C^6, C^8, C^9); 133.64 (s, C^4); 161.42 (d, C^7)
14	**3e** 0.95 (4.0)	**e** 0.55 (2.0)	**7e** (90) (*o*-chloro)	80	82/– [7]	4.27 (m, 4H, H^3); 4.70 (m, 4H, H^2); 7.05, 7.07, 7.26, 7.47 (4m, 8H, H^6, H^7, H^8, H^9)	70.56, 71.08 (2d, C^2, C^3); 84.74 (s, C^1); 126.25, 126.96, 130.33, 131.24 (4d, C^6, C^7, C^8, C^9); 132.21 (s, C^5); 136.07 (s, C^4)
15	**3f** 0.95 (4.0)	**2** 0.55 (2.0)	**7f** (75) (*m*-chloro)	65	182/183 [9]	4.20 (m, 4H, H^3); 4.40 (m, 4H, H^2); 7.03 (m, 8H, H^5, H^7, H^8, H^9)	67.72, 70.56 (2d, C^2, C^3); 84.69 (s, C^1); 123.74, 125.63, 125.79, 129.44 (4d, C^5, C^7, C^8, C^9); 134.23 (s, C^6); 139.26 (s, C^4)
16	**3g** 0.95 (4.0)	**2** 0.55 (2.0)	**7g** (70) (*p*-chloro)	50	188/192 [10]	4.24 (m, 4H, H^3); 4.45 (m, 4H, H^2); 7.13 (m, 8H, H^5, H^6, H^8, H^9)	67.63, 70.46 (2d, C^2, C^3); 84.93 (s, C^1); 126.90, 128.37 (2d, C^5, C^6, C^8, C^9); 131.45 (s, C^7); 136.08 (s, C^4)
17	**4b** 0.70 (4.0)	**2** 0.55 (2.0)	**7b** (80) (*o*-fluoro)	60	88/– [7]	See entry 11	
18	**4e** 0.77 (4.0)	**2** 0.55 (2.0)	**7e** (90) (*o*-chloro)	70	82/– [7]	See entry 14	
19	**4h** 2.83 (12.0)	**2** 0.55 (2.0)	**7h** (75) (*p*-bromo)	60	195/196 [11]	4.24 (m, 4H, H^3); 4.44 (m, 4H, H^2); 7.06, 7.27 (2m, 8H, H^5, H^6, H^8, H^9)	67.67, 70.59 (2d, C^2, C^3); 85.04 (s, C^1); 119.51 (s, C^7); 127.26, 131.31 (2d; C^5, C^6, C^8, C^9); 136.59 (s, C^4)

[a] Determined by ^{1}H NMR spectroscopy.

3. Experimental details

All reagents were purchased from Fluka and Aldrich Chemical Co. and used as received. 1,1'-Dibromoferrocene [14], 1,1'-diiodoferrocene [14] and $PdCl_2(dppf)$ [15] were prepared by published procedures. Solvents were dried by standard methods. All reactions were carried out under nitrogen. Melting points were obtained with a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 400 and 100 spectrometer (400 and 100 MHz).

3.1. *Preparation of ferrocene-1,1'-diboronic acid [6]*

To a stirred solution of ferrocene (1) (10 g, 54 mmol) in diethyl ether (200 ml) at room temperature was added a mixture of n-butyllithium (^{n}BuLi) (1.6 M in hexane, 75 ml, 120 mmol), TMEDA (18.1 ml, 120 mmol) and diethyl ether (100 ml). After 6 h stirring at room temperature, the suspension was added dropwise to a stirred and cooled (−78°C) solution of tributylborate (35 ml, 130 mmol) in diethyl ether (200 ml). The mixture was kept at −78° for 1 h, then allowed to warm up to room temperature and stirred for a further 12 h. After hydrolysis with 10% aqueous KOH (150 ml), the organic layer was extracted with aqueous KOH (4 × 100 ml). The combined aqueous layers were cooled in an ice-bath and acidified with dilute H_2SO_4 (10%). The precipitate was recovered by filtration, washed with water (500 ml), and dried (P_4O_{10}, 0.10 mbar). The crude material was purified by extraction with diethyl ether; yield 8.9 g (60%); m.p. 185°C (dec.) (Lit. [6]: 180°C; dec.). ^1H NMR (DMSO-d_6): δ 4.17 (m, 4H, H^3); 4.34 (m, 4H, H^2); 7.48 (s, 4H, OH). ^{13}C NMR (DMSO-d_6): δ 64.81 (s, C^1); 71.65 (d, C^3); 73.66 (d, C^2).

3.2. *Preparation of 1,1'-diphenylferrocene; method A*

A mixture of boronic acid, the aryl halide (see Table 1), toluene (20 ml), 2 M aqueous Na_2CO_3 (20 ml) and $Pd(PPh_3)_4$ (46 mg, 4.0×10^{-5} mol) was refluxed with vigorous stirring for 6 days. The organic layer was diluted with toluene (100 ml), washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed and the residue purified by column chromatography (silica gel, eluent: toluene/hexane (1:5)), followed by crystallization from low-boiling petroleum ether; m.p.: 152°C (Lit. [13a]: 152–153°C). ^1H NMR ($CDCl_3$): δ 4.19 (m, 4H, H^3); 4.45 (m, 4H, H^2); 7.14–7.32 (m, 10H, H^5, H^6, H^7). ^{13}C NMR ($CDCl_3$): δ 67.91 (d, C^3); 70.53 (d, C^2); 86.08 (s, C^1); 125.85 (d, C^7); 125.99, 128.23 (d, C^6, C^5); 138.16 (s, C^4).

3.3. *Preparation of 1,1'-diphenylferrocene and 1,1'-bis(halophenyl)ferrocenes; method B*

A mixture of boronic acid and the aryl halide (see Tables 1 and 2), DME (15 ml), 3 M aqueous NaOH (3 ml) and $PdCl_2(dppf)$ (30 mg, 4×10^{-5} mol) was refluxed with vigorous stirring for 6 days. Chloroform (200 ml) and water (50 ml) were added and the layers separated. The organic layer was washed with water (3 × 100 ml), dried ($MgSO_4$) and the solvent was removed. The crude product was purified as described above (method A). For yields, NMR spectra and melting points, see Table 2.

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