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Short Communication

Palladium-catalyzed formation of secondary and tertiary amines from aryl dihalides with air-stable ferrocenyl tri- and diphosphines: Synthesis and X-ray structure of efficient catalysts beyond [$PdCl_2$(DPPF)]

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ABSTRACT

Robust, air-stable tridentate and bidentate ferrocenylphosphines 1,2-bis(diphenylphosphino)-1′-(di*iso*propylphosphino)-4-*tert*-butylferrocene, **L5**, and 1,1′-bis(di*iso*propylphosphino)-3,3′-bis(tert-butyl)ferrocene, **L9**, combined with 1 mol% of [$PdCl(\eta^3\text{-}C_3H_5)]_2$ led to two new catalytic systems which allow the coupling of aniline derivatives with mono- and dihaloarenes to form functionalized diarylamines and triarylamines. The excellent selectivity of the reactions avoids the deleterious dehalogenation of the substrates and products. The X-ray structure characterization of the related complex [$PdCl_2$(**L9**)] is reported in which ligand **L9** in its *meso* form is significantly distorted.

1. Introduction

Arylamines are common building blocks of many biologically active natural products and organic materials. The first syntheses of arylamines were carried out by nitration of arenes followed by catalytic hydrogenation or a reduction with a metal salt. These procedures that employ strong acidic and oxidizing conditions are incompatible with many functional groups, and thus require the use of protective groups in multiple reaction step. The discovery of palladium-catalyzed aryl–amine bond forming reactions procedures has enlarged the availability of these important arylamine compounds [1–3]. The complex [$PdCl_2$(DPPF)] (DPPF = 1,1′-bis(diphenylphosphino)ferrocene) has been successfully employed as a pre-catalyst in the coupling of aryl halides with primary amine aniline derivatives [4]. This catalyst provided nearly quantitative yields for electron-rich, electron-poor, hindered or unhindered aryl bromides and iodides. The coupling of the secondary amine di-*n*-butylamine with 4-*tert*-butylbromobenzene was more difficult: only 40% of coupling product was obtained employing 5% [$PdCl_2$(DPPF)] and 15 mol% DPPF, a number of other systems giving better results [5–7]. The air-stability of ferrocenyl diphosphines, the steric control and chelating stabilization they provide, nevertheless renders this class of ligands very convenient for handling and use off-the-shelf [8, 9].

On the other hand, the use of air-stable robust ferrocenyl *poly*phosphines (tri- and tetradentate) as ligands in palladium-catalyzed C – C bond formation has led to a diverse range of highly efficient catalytic systems, which offer activities several orders of magnitude higher than DPPF-derived catalyst systems for cross-coupling reactions using electronically and/or sterically demanding organic halides [10–15]. The efficiency of ferrocenyl phosphines at low catalyst loading was also recently confirmed in the palladium-catalyzed C – O bond coupling for heteroarylether formation from functionalized phenols and chloroheteroarenes [16]. We envisioned that ferrocenylphosphine ligands (Fig. 1) might be useful for the coupling of aniline derivatives with bromoarenes, and especially concerning polyfunctionalized substrates, as well as for thereafter applications to the more difficult formation of triarylamines [17–21]. The valuable targets we identified are depicted in Fig. 2. The compounds of formula **A** may, for instance, open the access to the formation of bioactive carbazoles [22–24], while the compounds **B** and **C** are pertinent building blocks for construction of redox-active polytriarylamine compounds and materials

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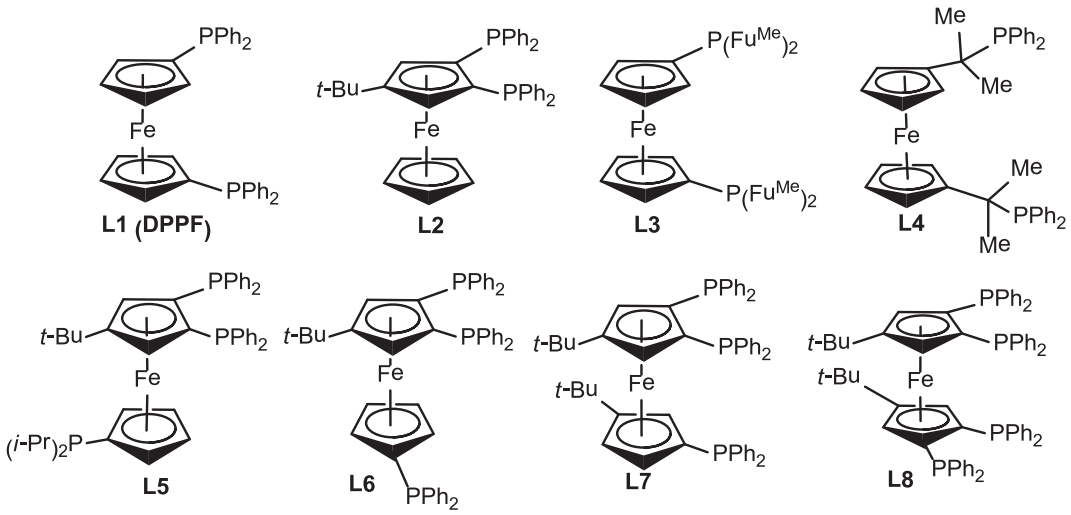


Fig. 1. Ferrocenylphosphines tested in C – N bond formation from 1,2-dibromobenzene.

[25–27]. Therefore, finding efficient and easy to handle catalytic systems for the synthesis of these species is timely.

2. Results and discussion

We hypothesized that backbone **A** may be the most difficult to synthesize because of selectivity and reactivity reasons (functionalization in *ortho*-position). Thus, we investigated the conditions of coupling of aniline with 1,2-dibromobenzene. Preliminary screening tests showed that no reaction proceeds in the absence of palladium, or in the presence of palladium but without any auxiliary ligand. However, encouraging screening experiments indicated that with 1 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 mol% of DPPF, the use of toluene as solvent, at 100 °C, in the presence of 1.4 equiv. of *t*-BuOK as base, selectively led to the conversion of 1,2-dibromobenzene (**2a**) into 2-bromodiphenylamine (**3a**) in about 30% yield. This amount of palladium and ligand is five to ten times lower, with conditions generally milder, than the current syntheses for the coupling of comparable substrates [28–33]. Under these conditions of base, solvent and temperature, the performances of phosphines **L2** to **L9** were also examined and compared to DPPF (Table 1).

The ligand dependency of this reaction was clearly established. Indeed, the ligands **L4** and **L7** were found fully inefficient (entries 4 and 7). While **L2** gave only a modest yield in **3a** (entry 2), the performances of **L3** match the moderate ones obtained with DPPF (entries 3 and 1, respectively). The conversion of **2a** was the most significant in reactions promoted by $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and ligands **L5**, **L6** and **L8**; however only **L5** gave a satisfactory selectivity in **3a** (entry 5) since the use of the two other ligands (entries 6 and 8) induces the formation in significant amount of diphenylamine by dehalogenation of **3a**. Further optimization of the catalytic process was focused thus on **L5** ligand as summarized in Table 2. The optimization of temperature (entries 1–3) indicated that reaction in refluxing toluene was beneficial. DBU as a base was inefficient (entry 4). Cation dependence was observed for the *tert*-butoxide bases, where *t*-BuONa (entries 5–8) was found to be more suitable than *t*-BuOK. This behavior has been observed before [34], and may result from the greater solubility of the sodium compound which was reported to be in toluene at 25 °C as *t*-BuONa, 6 wt.% and *t*-BuOK, 2.3 wt.% [34]. With these conditions in hands it was possible to significantly reduce the reaction time, which improves the final isolated yield (98%) by diminishing the dehalogenation of **3a**.

In the presence of an excess of aniline (3. equiv.), bis(amination) of 1,2-dibromobenzene takes place above 80% yields. GC/NMR monitoring clearly show that the first amination is selectively achieved at 98 yield% within 2 h, then followed by bis(amination) which is achieved at about 80% within 8 h. Interestingly, it appears thus that the coupling of the second equivalent of aniline to the intermediate monobromodiarylamine is much slower than the addition of the first equivalent of aniline to the 1,2-dibromobenzene. This is in contrast to previously reported results using the air-sensitive electron-rich monophosphine P(*t*-Bu)$_3$ [31].

The [Pd]/**L5** catalytic system was also used to examine the influence of the nature of the halide on the cross-coupling partner in the formation of the building block **A** (Fig. 3). We found that within 2 h the heterodihaloarenes **2b** and **2c** are efficiently coupled to aniline with high yield. From **2b** the reaction is perfectly selective with only arylation at the iodide position; this shows the influence of the first substitution in *ortho*-position on the reactivity of the

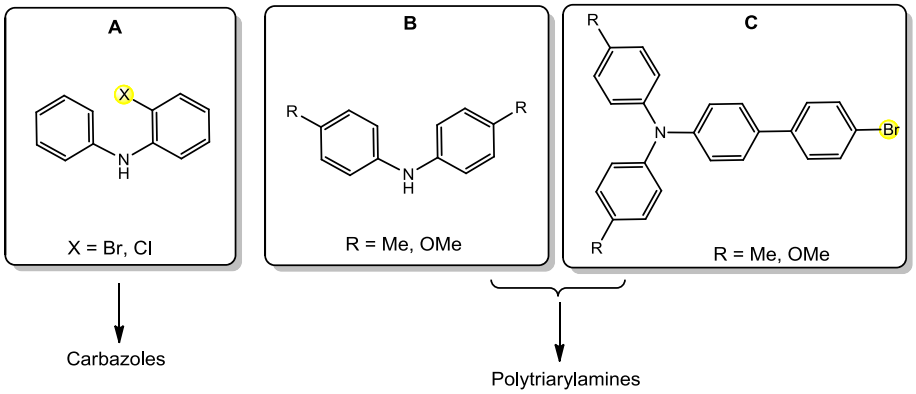
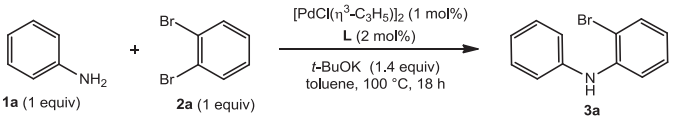


Fig. 2. Targeted diaryl and triaryl amines building blocks.

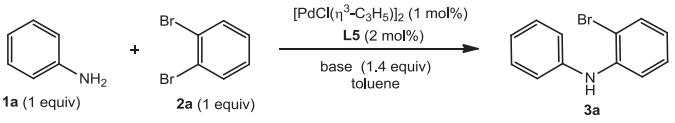
Table 1
Screening of [Pd/Ligand] catalyst activity.



Entry	Ligand	Conversion of **2a** (%)	Yield in **3a** (%)
1	**L1** (= **DPPF**)	28	25
2	**L2**	14	12
3	**L3**	32	30
4	**L4**	<5	<5
5	**L5**	55	50
6	**L6**	40	30
7	**L7**	<5	<5
8	**L8**	50	25

Conditions: [Pd]/**L** (0.02 equiv.), aniline **1a** (1 equiv.), 1,2-dibromobenzene **2a** (1 equiv.), *t*-BuOK (1.4 equiv.), 100 °C, 18 h.

Table 2
Base, solvent and temperature optimization.



Entry	Base	Temperature	Time	Conversion of **2a** (%)	Yield in **3a** (%)
1	*t*-BuOK	100	18	55	50
2	*t*-BuOK	85	20	30	30
3	*t*-BuOK	115	18	92	79
4	DBU	115	18	<5	<5
5	*t*-BuONa	115	16	100	73
6	*t*-BuONa	115	8	100	79
7	*t*-BuONa	115	4	100	88
8	*t*-BuONa	115	2	100	98

Conditions: [Pd]/**L** (0.02 equiv.), aniline **1a** (1 equiv.), 1,2-dibromobenzene **2a** (1 equiv.), base (1.4 equiv.).

resulting compound. Gratifyingly, we observed that the system is even suitable to selective coupling of 1,2-dichlorobenzene (**2d**), albeit in longer reaction time (16 h) with slightly lower yields (90%). The [Pd]/**L5** catalyst system was then successfully used for the formation of compounds **4a** and **4b** (type **B**). The compound bis(4-methylphenyl)amine (**4a**) was synthesized in 84% yield by cross-coupling 4-methylaniline with 4-bromotoluene (Fig. 3). In similar fashion, bis(4-methoxyphenyl) amine (**4b**) was produced in 87% yield by coupling the *p*-anisidine with 4-bromoanisole. In comparison, by using $Pd_2(dba)_3$ (1 mol%) and DPPF (3 mol%) the conversion obtained were 79% and 50%, respectively.

With the diarylamines **4a** and **4b** in hand we applied the same conditions with the view of generating the triarylamines **5a** and **5b** by further cross-coupling of the secondary amines with the dihalide 4-bromo-4′-iodobiphenyl (Fig. 4). Unfortunately, while our optimized system [Pd]/**L5** was found very effective for formation of functionalized secondary amines (Fig. 3) it was inefficient for properly producing the tertiary amines **5a** (<5%) and **5b** (0%) (Fig. 4). We then turned back to our library of ferrocenyl phosphine ligands considering some of the properties of **L5**, and in particular the combination of *iso*-propyl groups on phosphorus and the control of conformation due to the presence of *tert*-butyl groups on the ferrocene backbone, was identified as specific to this ligand compared to **L2**–**L4**, **L6**–**L8**. Thus, the recently synthesized diphosphine **L9** [34] was tested in the synthesis of triarylamines (Fig. 4), and was found to be appropriate to produce in good yield the electron-rich triarylamine **5b** (72%), in comparison, by using $Pd_2(dba)_3$ (1 mol%) and DPPF (3 mol%) the conversion obtained of **5b** were 29%. It also led in moderate yield to **5a** (27%).

To better assess the structures of the ligand and palladium precatalyst, single crystals of the [$PdCl_2$**L9**] complex suitable for X-Ray characterization were grown. The molecular structure of the complex is depicted in Fig. 5 and confirmed the *meso* nature of the diphosphine (Fig. 5).

The palladium complex is embedded in a square planar environment, in which a large bite angle P1-Pd-P2 = 101.35° is observed;

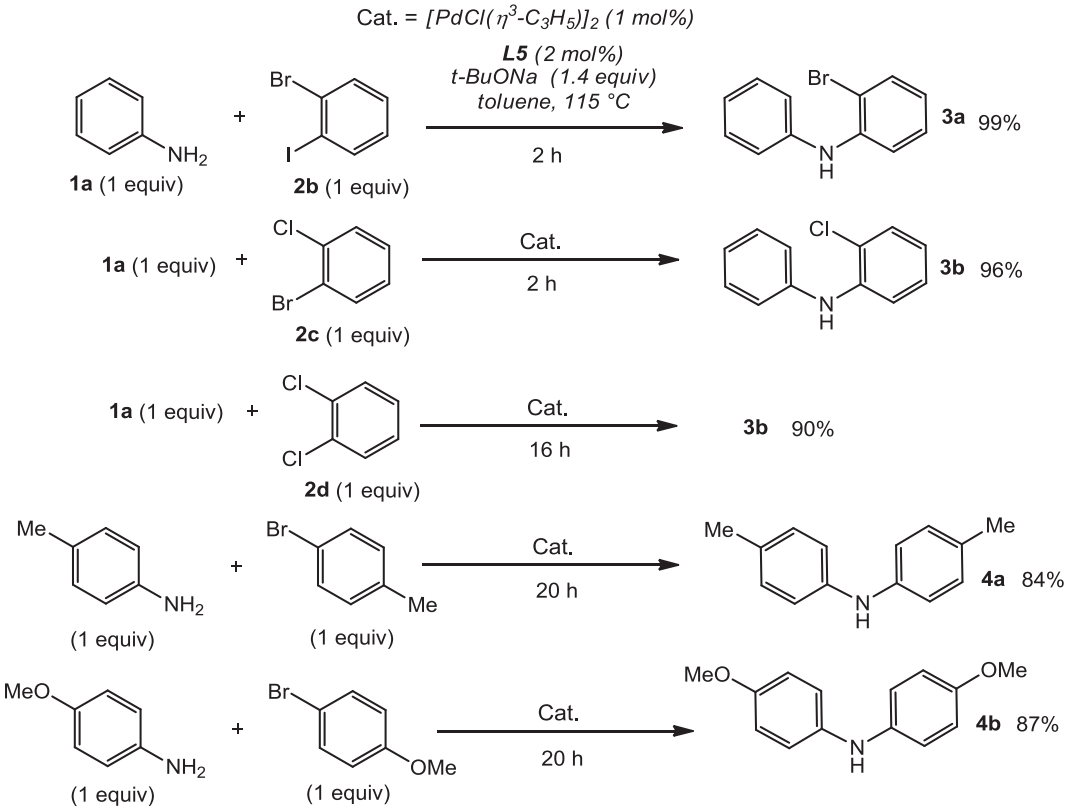


Fig. 3. Synthesis of targets **A** and **B** from [Pd]/**L5**.

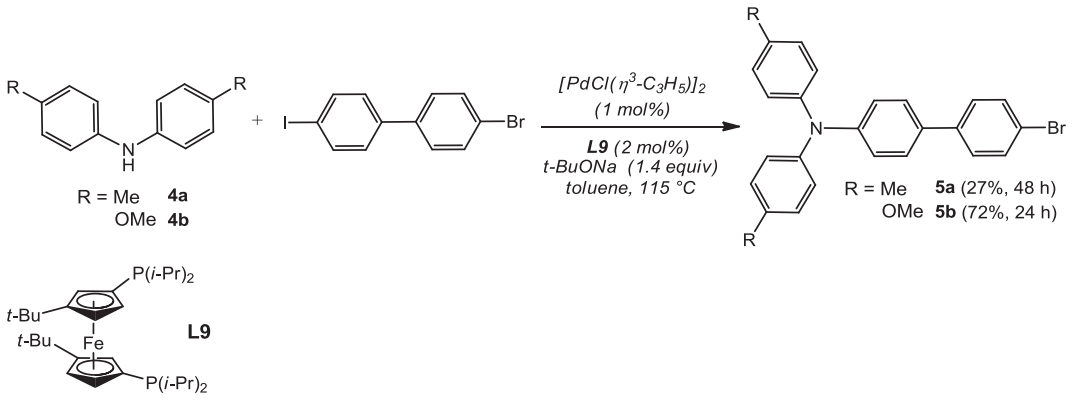


Fig. 4. Ferrocenyl diphosphine **L9** for halogenated triaryl amine formation.

this is likely favorable for reductive elimination of triarylated amines at palladium. In [$PdCl_2$**L9**] the deformation of the ferrocene backbone is noticeable with a Ct1-Fe-Ct2 = 173.63(15)°, which is significantly distorted from the expected ideal angle of 180°. As shown in the view from above, despite the steric hindrance generated at *tert*-butyl groups a small torsion angle (below 32°) is observed, i.e. P1-Ct1-Ct2-P2 = −29.93(8).

In summary we disclosed herein two new catalytic systems based on air-stable robust di- and tridentate ferrocenyl polyphosphines **L5** and **L9**, which allow the coupling of aniline derivatives with chloro or bromoarenes to form diarylamines and triarylamines functionalized with halides. The selectivity of the reactions allows the use of mild reaction conditions and short reaction times, avoiding dehalogenation of the substrates and products. The X-ray structure characterization of the related complex [$PdCl_2$(**L9**)] was also reported.

3. Experimental

The reactions were carried out in oven-dried (115 °C) glassware under an argon atmosphere using Schlenk and vacuum-line techniques. The solvents were distilled over appropriate drying and deoxygenating agents prior to use. Commercial aryl halides and aniline derivatives were used without further purification. ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded in $CDCl_3$. All the ferrocenylphosphine ligands were synthesized by methods reported in the literature [10–16, 35], and are stored and weighed under air without special precautions. The ferrocenyl ligand **L5** is commercially available from STREM Chemicals under the name HiersoPHOS-4.

4.1. Synthesis and characterization of [$PdCl_2$**L9**]

A mixture of 1,1′-bis(di*iso*propylphosphino)-3,3′-di-*tert*-butyl ferrocene (304 mg, 0.573 mmol) and $PdCl_2$ (110 mg, 0.619 mmol) was heated in refluxing THF (10 mL) for 17 h. The brown solution was filtrated through silica, and the column washed with dichloromethane. The solvent was evaporated from the combined organic fractions under vacuum to give 160 mg of the complex (39%). Fractional crystallization allows recovering pure *meso* complex.

^{1}H NMR ($CDCl_3$, *rac* + *meso*): δ(ppm) = 0.58 (dd, 6H, $^{3}J_{PH}$ = 7 Hz, *i*-Pr-CH_3), 0.85 (p-t, 6 H, $^{3}J_{PH}$ = 6 Hz, *i*-Pr-CH_3), 1.11 (s, 18 H, *t*-Bu, minor isomer), 1.16 (s, 18H, *t*-Bu, major isomer), 1.60 (m, 12 H, *i*-Pr-CH_3), 2.87 (hept, 2H, $^{3}J_{HH}$ = 7 Hz, *i*-Pr-C*H*), 3.07 (hept, 2H, $^{3}J_{HH}$ = 7 Hz, *i*-Pr-C*H*), 4.25, 4.33, 4.38 (m, 2H each, *H*-Cp, major isomer), 4.15, 4.44 (m, *H*-Cp, minor isomer). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ (ppm) = 62.15 (s, 2 P-*i*-Pr_2, minor isomer 17%, *racemic* compound), 59.35 (s, 2 P-*i*-Pr_2, major isomer 83%, *meso* compound). ^{13}C NMR ($CDCl_3$): δ (ppm) = 108.3 (s, 2C, Cp*C*-*t*-Bu, major isomer 83%), 106.8 (s, 2C, Cp*C*-*t*-Bu, minor isomer 17%), 74.0 (s, 2C, Cp*C*-Pi-Pr_2), 73.4 (s, 2C, Cp-*C*H), 70.8 (s, 2C, Cp-*C*H, major isomer), 69.9 (s, 2C, Cp-*C*H, minor isomer), 67.9 (s, 2C, Cp-*C*H, major isomer), 67.3 (s, 2C, Cp-*C*H, minor isomer), 30.6 (s, 6C, *t*-Bu-(CH_3)$_3$, major isomer), 30.5 (s, 6C, *t*-Bu-(CH_3)$_3$, minor isomer), 29.6 (s, 2C, *C*(CH_3)$_3$, minor isomer), 29.4 (s, 2C, *C*(CH_3)$_3$, major isomer), 27.8 (m, 2C, *C*H-*i*-Pr), 27.7 (m, 2C, *C*H-*i*-Pr), 27.4, 27.2 (m, 2C each, *C*H-*i*-Pr, minor isomer), 20.5 (s, 2C, *C*H_3-*i*-Pr), 20.3 (s, 2C, *C*H_3-*i*-Pr), 19.4 (s, 2C, *C*H_3-*i*-Pr), 18.9 (s, 2C, *C*H_3-*i*-Pr), 20.8, 20.6, 19.10 (m, 2C each, *C*H_3-*i*-Pr, minor isomer). ESI-MS: $[M - Cl]^+$: m/z = 671.16259, simulated = 671.16225, δ = 2.140 ppm; $[M + Na]^+$: m/z = 729.12005, simulated = 729.12062, δ = 0.375 ppm.

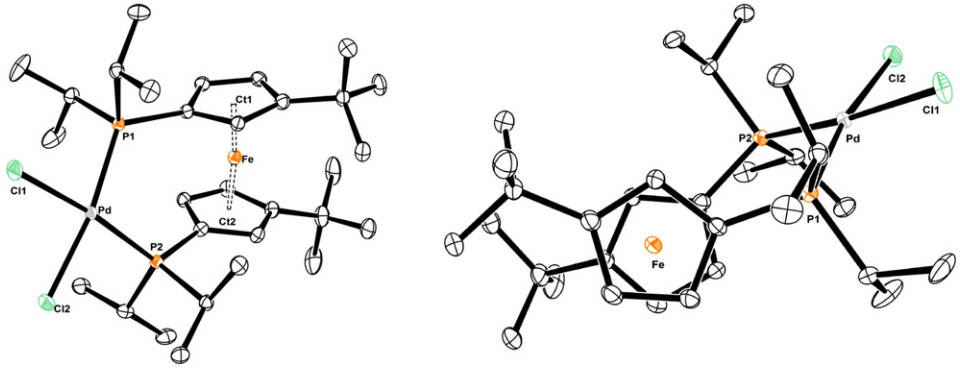


Fig. 5. Ortep molecular views of palladium dichloride stabilized by the coordination of diphosphine **L9** (hydrogen atoms are omitted for clarity). Selected distances (Å) and angles (°): Fe-Ct1 = 1.663(3); Fe-Ct2 = 1.668(3); Ct1-Fe-Ct2 = 173.63(15); P1-Pd-Cl1 = 85.85(3); P2-Pd-Cl2 = 85.76(3); P1-Pd-P2 = 101.35(3); Cl1-Pd-Cl2 = 87.19(3); P1-Ct1-Ct2-P2 = −29.93(8); and P1…P2 = 3.5318(11).

4.2. Catalytic cross-coupling reactions

In a Schlenk tube equipped with a stirring bar, the aniline derivative (2 mmol, 1 equiv.), the haloarene (2 mmol, 1 equiv.), the complex $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.02 mmol), **L5** or **L9** (0.04 mmol), and *t*-BuONa (2.8 mmol, 1.4 equiv.) were introduced. The tube was purged several times with argon. Toluene (9 mL) was added to the mixture. The Schlenk tube was placed in an oil bath at 115 °C and reactants were allowed to stir under reflux for 2 to 20 h. After filtration, the solvent was evaporated and the residue was charged onto a silica gel column for chromatography.

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