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Palladium C–N bond formation catalysed by air-stable robust polydentate ferrocenylphosphines: a comparative study for the efficient and selective coupling of aniline derivatives to dichloroarene†

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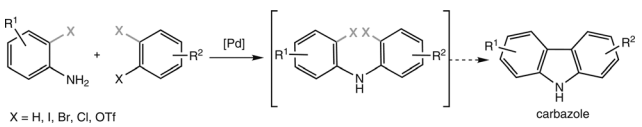
The arylation of aniline derivatives with dichloroarenes under a low palladium content (below the currently used 5 to 10 mol%) was studied using nine different ferrocenylphosphine ligands, including the easily accessible 1,1′-bis(diphenylphosphino)ferrocene, DPPF. The electron-enriched air-stable tridentate ferrocenylpolyphosphine 1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-*tert*-butylferrocene, **L5**, employed in 2 mol% in combination with 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ allows an efficient and selective coupling, while such demanding substrates currently induce chloroarene homocoupling and/or dehalogenation processes. The scope and limitation of the optimized system are explored, with a focus on electron-poor fluoroanilines (deactivated nucleophiles) and electron-rich methylated and methoxylated dichlorobenzenes (deactivated electrophiles).

Introduction

The palladium-catalysed coupling of aniline derivatives with haloarenes is an attractive first step to intermolecularly form carbazole derivatives from cheap and easily available substrates (Scheme 1).[1,2] Carbazoles are fused heterocyclic aromatic molecules displaying powerful applications in medicine[3–6] and materials science.[7–9] The current approaches to this sp^2 C–N bond formation, which is especially challenging when bromo- and chloroarenes are employed, are based on the use of electron-rich and air-sensitive monodentate phosphines such as $P(t\text{-Bu})_3$[10,11] and PCy_3[12] in catalytic systems in which 5 to 10 mol% of palladium and ligands are needed. The use of norbornene (25 mol%) in the Pd oxidative coupling of protected bromoanilines and iodoarenes[13] and the employment of the biphenyl monophosphine X-Phos (15 mol%) for the coupling of aryl triflates have also been reported.[14] In these studies, the C–N bond formation step has not been studied by itself but in a cascade or in one-pot processes. While acknowledging the valuable work in this area, we believe that progress in catalysis science and technology, in order to reach industrial application, also lies in minimizing the amount of palladium (for cost and environmental reasons) and providing catalytic systems in which phosphine oxide formation does not hamper the general expediency on a large scale. The use of air-stable robust ferrocenylphosphines as ligands in palladium-catalysed C–C bond formation has led to highly efficient catalytic systems in which the amount of palladium and ligands was decreased by several orders of magnitude for cross-coupling reactions using demanding organic halides.[15–17] The efficiency of ferrocenylpolyphosphines at low catalyst loading was also been recently confirmed in the palladium-catalysed C–O bond coupling for heteroarylether formation from functionalized phenols and chloroheteroarenes.[18] We envision that ferrocenylphosphine ligands (Fig. 1) might be useful in the coupling of aniline derivatives with bromo- and chloroarenes at lower catalyst loading, especially concerning polyfunctionalized substrates with functionality at the *ortho*-position.[17]

We report herein the higher efficiency in the C–N coupling of polyfunctionalized dichloroarenes with anilines of an air-stable tridentate ferrocenylpolyphosphine suitable under



Scheme 1 General pathway to carbazoles *via* Pd-catalysed coupling of anilines to haloarenes.

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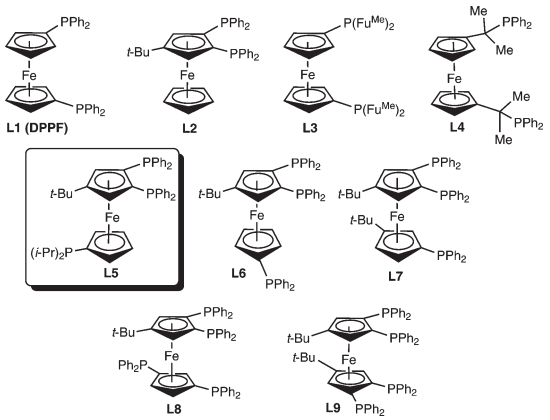


Fig. 1 Polydentate ferrocenylphosphines probed as ligands in C–N palladium coupling.

optimized conditions to be used with 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Comparison with eight other air-stable diphosphines, triphosphines and tetraphosphines of the same class indicates that the selectivity of the coupling of dichloroarene to aniline derivatives by palladium catalysis is possible as long as homocoupling and/or dehalogenation of chloroarenes is avoided. Some limitations of the catalytic system in terms of scope and selectivity are also established.

Results and discussion

In order to investigate our hypothesis we first explored the performance of the air-stable and readily available diphosphine 1,1′-bis(diphenylphosphino)ferrocene, DPPF (**L1**), in the coupling of aniline with 1,2-dichlorobenzene (Table 1).

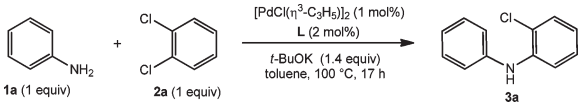
In toluene in the presence of 1.4 equiv. *t*-BuOK, no cross-coupling reaction occurred in the absence of palladium and the phosphine ligand (entry 1). Under the same conditions the use of 5 mol% $Pd(OAc)_2$ or $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in the absence of auxiliary phosphine was also inefficient (entries 2 and 3). Satisfactorily, the formation of **3a**, albeit in modest 15–20% yield, was observed upon addition of 2 mol% DPPF to the palladium sources selected (entries 4 and 5).

Further screening of the catalytic conditions indicated that using sodium carbonate as base was completely inefficient (entries 6 and 7). The use of DMF while increasing the conversion of **1a** also favoured the dehalogenation of **3a** to diphenylamine (entry 8). Increasing the loading of palladium and the ligand to 10 mol% only favoured the homocoupling reaction, leading to 2,2′-dichlorobiphenyl followed by dehalogenation to 1-chloro-2-phenylbenzene and biphenyl (entry 9); these side reactions were also observed upon increasing the temperature to toluene reflux (entry 10). Thus, DPPF was found rather limited for efficient and selective coupling of **1a** with **2a**.

On the basis of the most selective conditions identified for DPPF (Table 1, entry 4) we compared the performance of a set of bidentate, tridentate and tetradentate ferrocenylphosphines **L2**–**L9** (Fig. 1). The results of the screening experiments are reported in Table 2.

The selectivity of coupling to **3a** was conserved for all of the ligands used, except for the electron-poor diphosphine **L3**

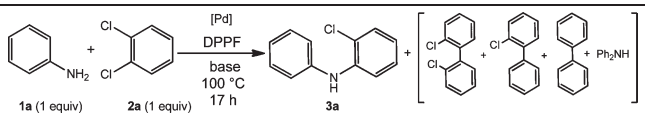
Table 2 Performance of polydentate ferrocenylphosphines **L1**–**L9** in the palladium-catalysed arylation of aniline with 1,2-dichlorobenzene[a]



Entry	Ligand	Conversion (%)	Yield in **3a** (%)
1	**L1**	25	20
2	**L2**	12	10
3	**L3**	30	15
4	**L4**	16	13
5	**L5**	55	52
6	**L6**	15	13
7	**L7**	<5	—
8	**L8**	<5	—
9	**L9**	<5	—

[a] Conditions: [Pd]/**L** (0.02 equiv.), aniline **1a** (1 equiv.), 1,2-dichlorobenzene **2a** (1 equiv.), *t*-BuOK (1.4 equiv.), 100 °C, 17 h.

Table 1 Influence of reaction conditions on the palladium-catalysed arylation of aniline with 1,2-dichlorobenzene promoted by DPPF (**L1**)[a]



Entry	Pd source (mol%)	**L1** (mol%)	Base/solvent	Conversion (%)	Yield in **3a** (%)
1	—	—	*t*-BuOK/toluene	0	0
2	$Pd(OAc)_2$ (5)	—	*t*-BuOK/toluene	0	0
3	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5)	—	*t*-BuOK/toluene	0	0
4	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1)	2	*t*-BuOK/toluene	25	20
5	$Pd(OAc)_2$ (1)	2	*t*-BuOK/toluene	20	16
6	$Pd(OAc)_2$ (1)	2	Na_2CO_3/toluene	0	0
7	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1)	2	Na_2CO_3/toluene	0	0
8	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1)	2	*t*-BuOK/DMF	40	15
9	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5)	10	*t*-BuOK/toluene	29	20
10	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1)	2	*t*-BuOK/toluene	40[b]	20

[a] Conditions: [Pd]/**L1** (0.01 to 0.1 equiv.), aniline **1a** (1 equiv.), 1,2-dichlorobenzene **2a** (1 equiv.), base (1.4 equiv.), 100 °C, 17 h. [b] 115 °C.

(entry 3). The sterically released **L4** was inefficient (entry 4).[19] We were glad to observe that the results unambiguously indicated that the tridentate ferrocenylpolyphosphine **L5** was by far the most efficient and selective auxiliary for the coupling we targeted, with a yield of 52% in **3a** for a conversion of 55% of **2a** (entry 5). The diphosphines **L2** (which undergoes a 1,2-coordination to palladium with a smaller P-bite angle) and **L3** were found less efficient than DPPF (entries 2, 3 and 1, respectively). The conformationally constrained triphosphine and tetraphosphine **L7**–**L9** (which hold *t*-butyl groups hampering the free rotation of the ferrocene backbone) were found completely inefficient under these conditions. Conversely, the triphosphine **L6**, which is structurally close to **L5**, selectively led to a modest yield in C–N coupling.

While we find triphosphine **L5** a suitable auxiliary for the selective arylation of aniline with 1,2-dichlorobenzene at lower Pd-catalyst loading,[20] we performed further optimization studies to improve the yield. These optimization processes, which are summarized in Table 3, were focused on the base and the reaction temperature since toluene solvent allows conservation of excellent selectivity. The yield in **3a** was slightly improved by using the Pd/**L5** system with *t*-BuOK at higher temperature, 115 °C (see entries 1 and 2); this dependence in temperature was confirmed by the reduced yield obtained at 85 °C under identical conditions (entry 3). At 100 °C the use of DBU and *t*-BuONa did not improve the yields in **3a** (entries 4 and 5, respectively). However, combining *t*-BuONa as the base and toluene at reflux significantly improved the yield in **3a** with a full conversion obtained within 16 h (entry 6, isolated yield 90%). The highest reaction rate which was achieved by using these conditions was confirmed with 88% conversion in 8 h, and 68% conversion in 4 h (entries 7 and 8). In comparison, when DPPF was used under identical temperature and solvent conditions with *t*-BuONa for 24 h, a conversion of only 77% of the aniline was obtained with a yield of 69% in **3a** and 8% dehalogenation of **3a**. This indicates a much slower kinetics, which is detrimental to the selectivity regarding the dehalogenation process.

Using **L5** a careful tuning of the reaction time is important to optimize the yields since after 24 h of reaction the yield in **3a** dropped to 60% with about 35% dehalogenation product of **3a** as evidenced by ^{1}H NMR (δN*H* = 5.75 ppm against 6.03 for **3a**). In agreement, we observed that in the presence of excess aniline (3 equiv.), bis(amination) takes place over longer reaction times. Thus, it appears that the coupling of the first equivalent of aniline is much faster than the activation of the second chlorine atom for amination.[21] This explains the better results of selectivity obtained in monoamination for **L5**.

With a satisfactory palladium-based system identified, a performance survey of Pd/**L5** in the coupling of 1,2-dichlorobenzene with various aniline derivatives was conducted, which is reported in Table 4.

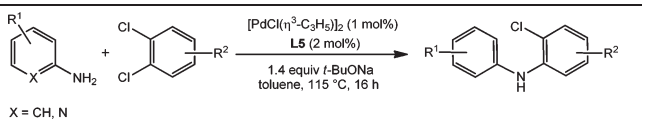
The introduction of fluorine atoms into medicinal compounds generally improves membrane transport, general bioavailability, solubility, and metabolic stability compared to non-fluorinated analogues. Therefore, fluorinated arenes are present not only in a number of important pharmaceuticals, but also in agrochemicals, and are of general interest in PET molecular imaging.[22] We focused our attention to the arylation of fluorinated anilines, which can be, as electron-poor nucleophiles, deactivated substrates for such C–N bond formation. Gratifyingly, the catalytic system tolerated the introduction of a fluoro group in *ortho*, *meta* or

Table 3 Influence of the base and temperature on **3a** synthesis using the system Pd/**L5**[a]

Entry	Base	Temp. (°C)	Time (h)	Conversion (%)	Yield in **3a** (%)
1	*t*-BuOK	100	17	55	52
2	*t*-BuOK	115	17	68	57
3	*t*-BuOK	85	17	25	25
4	DBU	100	17	—	—
5	*t*-BuONa	100	17	55	52
6	*t*-BuONa	115	16	98	90
7	*t*-BuONa	115	8	88	78
8	*t*-BuONa	115	4	68	58

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

Table 4 Scope of the catalytic system Pd/**L5** for the arylation of aniline derivatives with 1,2-dichlorobenzene[a]



Entry	Amine	Dichloride	Product	Yield[b] (%)
1	**1a**	**2a**	**3a**	90
2	**1b**	**2a**	**3b**	98
3	**1c**	**2a**	**3c**	96
4	**1d**	**2a**	**3d**	99
5	**1d'**	**2a**	**3d'**	(62)
6	**4**	**2a**	**5**	25 (90)[c]
7	**6**	**2a**	**7**	0[c]
8	**8**	**2a**	**9**	0[c]
9	**10**	**2a**	**11**	24 (44)[c]

[a] Conditions: [Pd]/**L** (0.02 equiv.), amine **1a** (1 equiv.), dichloride **2a** (1 equiv.), toluene, *t*-BuONa (1.4 equiv.), 115 °C, 16 h. [b] Isolated yields of two or more runs (GC/^{1}H NMR yields). [c] 22 h.

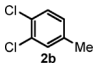
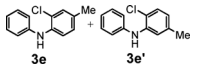
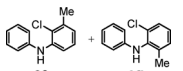
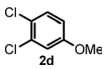
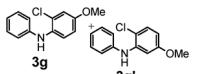
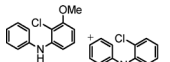
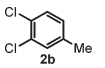
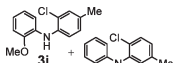
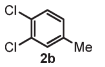
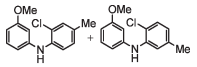
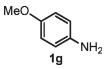
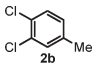
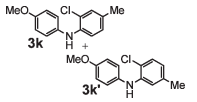
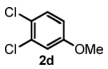
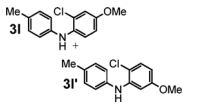
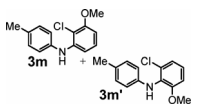
para position since products **3b**–**3d** were obtained in high yields (Table 4, entries 2–4). The conversion of electron-donating *p*-toluidine was also achieved in 88% yield within 16 h with a fairly good 62% yield (entry 5) in **3d′**; however, the dehalogenation product of **3d′** (26%) lowered the yield.

We also tested other amines having aromatic heterocycles such as 2-aminopyridine **4** and 2-aminothiazole **8**. Compound **4** was satisfactorily converted into **5**, but due to purification problems was isolated in only 25% yield (Table 4, entry 6). Aminopyrimidine **6** and aminothiazole **8** did not react (entries 7–8). Tertiary amine **11** was isolated in only 24% yield (entry 9) due to a partial conversion of the reagents into unidentified products and its partial dehalogenation. Additionally, we checked that the coupling of 1,2-dibromobenzene was also possible with our system, and predictably **3a** was obtained in excellent 96% yield within only 2 h.[21] Clearly, the system is efficient for iodo- and bromoarenes; however, for cost reasons the coupling of dichlorobenzenes is more valuable, even if more difficult. Interestingly, the catalytic system we found did not lead to any trace of carbazole cyclization, and thus is complementary to a few domino-reactions previously reported.[10–14]

With the view of further exploring the limitations of this catalytic system we examined the coupling of structurally more challenging substrates mainly not explored in the investigations which have been described to date. In particular, the coupling of functionalized dichloroarenes is of interest due to the regioselectivity issues which may occur. Electron-rich dichloroarenes were chosen because of their deactivation effect on C–Cl oxidative addition on palladium. As shown in Table 5 many various structures are thus accessible following this method with, in some cases, a fairly good to high regioselectivity (up to 1 : 10). We unfortunately often ended with mixtures in which the purification of the compounds by standard chromatographic methods was very difficult. Clearly, besides the efficiency and regioselectivity of the system, we expect further progress in the separation process of these valuable isomers.

The coupling of aniline with 4-methyl-1,2-dichlorobenzene and 3-methyl-dichlorobenzene give a 3 : 1 mixture of products **3e** and **3e′**, and **3f** and **3f′**, respectively, in about 70% isolated yield after workup (Table 5, entries 1 and 2: 51% **3e**, 17% **3e′**, 49% **3f**, 17% **3f′**). Comparatively, the effect on the regioselectivity of the arylation reaction of a methoxy group positioned on arenes is much stronger. Indeed, while the arylation of aniline with 4-methoxy-1,2-dichlorobenzene gives a 1 : 1 mixture of **3g** and **3g′** in 59% yield (entry 3: 31% **3g**, 28% **3g′**), the use of 3-methoxy-1,2-dichlorobenzene leads to **3h′** with high selectivity (60% yield, entry 4). The coupling of 4-methyl-1,2-dichlorobenzene with anilines methoxylated in various positions is also possible, albeit the selectivity is fairly low (1 : 2 in favour of **3i′**–**3k′**, entries 5–7). In addition the separation from unconverted materials is very difficult. Finally, the coupling of 4-methylated aniline with 3-methoxy-1,2-dichlorobenzene and 4-methoxy-1,2-dichlorobenzene proceeds satisfactorily with a good selectivity (entries 8 and 9). When the chlorine atom is at the *ortho* position to the methoxy group, the regioselectivity is up to 1 : 6 in favour of **3m′** (*vs.* **3m**), in agreement with what was observed for the formation of **3h′** (*vs.* **3h**).

Table 5 Coupling of polyfunctionalized substrates using 2 mol% Pd/**L5**[a]

Entry	Amine	Dichloride	Product(s)	Yield (%) / (selectivity)
1	 **1a**	 **2b**	 **3e** **3e'**	68 (3 : 1)
2	 **1a**	 **2c**	 **3f** **3f'**	66 (3 : 1)
3	 **1a**	 **2d**	 **3g** **3g'**	59 (1 : 1)
4	 **1a**	 **2e**	 **3h** **3h'**	60 (1 : 10)
5	 **1e**	 **2b**	 **3i** **3i'**	85 (1 : 2)[b]
6	 **1f**	 **2b**	 **3j** **3j'**	79 (1 : 2)[b]
7	 **1g**	 **2b**	 **3k** **3k'**	71 (1 : 2)[b]
8	 **1h**	 **2d**	 **3l** **3l'**	55 (1 : 6)[b]
9	 **1h**	 **2e**	 **3m** **3m'**	80 (1 : 5)

[a] Conditions: [Pd]/**L** (0.02 equiv.), amine **1a** (1 equiv.), dichloride **2a** (1 equiv.), toluene, *t*-BuONa (1.4 equiv.), 115 °C, 20 h. [b] Yields and selectivity were determined by consistent GC and ^{1}H NMR analyses.

A relevant question is the underlying reasons for the better efficiency of **L5** over the other ferrocenyl di-, tri- and tetraphosphines in the arylation of aniline with dichlorobenzene. Based on our previous DFT[18] and kinetic investigations,[23] which were respectively focused on the activity of ferrocenylpolyphosphines in the reductive elimination (RE) and oxidative addition (OA) to palladium, we propose the catalytic cycle shown in Fig. 2.

This cycle includes the two crucial intermediates **I1** and **I2**. Indeed, the tridentate phosphine stabilizes the Pd^0 species **I1**,[18,23] while the small bite angle due to 1,2-P phosphine coordination favours the OA of chloride substrates. Inversely, this type of small bite angle coordination strongly disfavours the RE step (see the poor performance of ligand **L2**). The isomerization to palladium complex **I2**, which is embedded into a 1,1′-P coordination with a much larger bite angle, may be the preferred pathway for an efficient RE of the arylated amine. This kind of isomerization (or Pd centre shuttling) from 1,2-P to 1,1′-P coordination for Pd(II) complexes has

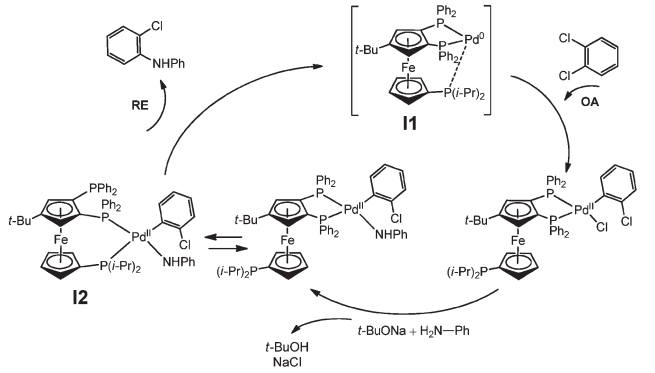


Fig. 2 Catalytic cycle of C–N coupling with Pd/**L5** favouring both chloroarene OA and biarylamine RE.

been previously calculated as not only possible but also energetically favoured,[18] and experimentally documented by NMR spectroscopy[24] and X-ray crystallography.[18] Finally, the donating effect of the phosphino group (i-Pr)$_2$P– also clearly helps the reaction to smoothly proceed (see for comparison the performance of **L6**, Table 2, entry 6). This general behaviour is obviously not possible for any of the other ferrocenylphosphines tested in the present study.

Conclusions

The air-stable tridentate ferrocenylpolyphosphine 1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-*tert*-butylferrocene, **L5**, employed in 2 mol% in combination with 1 mol% [PdCl(η^3-C$_3$H$_5$)]$_2$ in toluene with *t*-BuONa as base constitutes an efficient and selective system for the coupling of aniline derivatives with dichlorobenzene. This amount of palladium/ligand is the lowest reported to date for such demanding coupling. This catalytic system is several times faster when dibromoarenes are employed for the C–N coupling. This cross-coupling of demanding chlorobenzene substrates generally induces homocoupling or dehalogenation processes when other ferrocenylphosphines, solvents or bases are used. The scope and limitation of the optimized system were reported, showing good efficiency for the coupling of electron-poor fluoroanilines (deactivated nucleophiles) and electron-rich methylated and methoxylated dichlorobenzenes (deactivated electrophiles).

Experimental

General remarks

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, ^{19}F and ^{13}C NMR spectra were recorded in CDCl$_3$ using a 300 MHz Bruker Avance, unless otherwise stated. GC and GC-MS analyses were achieved on a Supelco equity-5 capillary column using a Shimadzu GC-2014 for gas chromatography or on an HP-5 capillary column (30 m) for GC-MS. All of the ferrocenylphosphine ligands were synthesized using the reported literature methods. The ferrocenylpolyphosphine ligands are commercially available from STREM Chemicals under the name HiersoPHOS. All ferrocenylphosphines were stored and weighed under air without special precautions.

Synthesis of triphosphine L5

A solution of (Ph$_2$P)$_2$Cp(*t*-Bu)Li (1.85 g, 3.7 mmol) in 20 mL of THF was added at −40 °C to a stirred suspension of anhydrous FeCl$_2$ (0.45 g, 3.55 mmol) in 20 mL of THF. After 2 h, 20 mL of THF solution of (i-Pr$_2$P)$_2$CpLi (0.67 g, 3.55 mmol) was added to the mixture. The THF solvent was evaporated *in vacuo* and the residue was refluxed in 40 mL of toluene for 3 h. From the cooled reaction mixture, the crude product was filtered off and purified by chromatography to provide 1.80 g (70% yield) of **L5**. Spectroscopic data were in agreement with those reported in the literature.[15b]

^{1}H NMR (400.13 MHz, CDCl$_3$): δ = 7.73 (m, 4H, Ph), 7.40 (m, 6H, Ph), 7.12–6.95 (m, 10H, Ph), 4.21 (t, 2H, J_{HP} = 1.2 Hz, 3,5*H*Cp), 4.17 (t, 2H, $^3J_{HH}$ = 2.0 Hz, 3′,4′(or 2′,5′)*H*Cp), 3.96 (m, 2H, J_{HP} < 2.0 Hz, $^3J_{HH}$ = 2.0 Hz, 2′,5′(or 3′,4′)*H*Cp), 1.53 (hept(d), 1H, $^2J_{HP}$ = 2.6 Hz, $^3J_{HH}$ = 7.0 Hz, C*H*^{i}Pr), 1.38 (s, 9H, ^{t}Bu), 0.93 (dd, 6H, $^3J_{HP}$ = 12.8 Hz, $^3J_{HH}$ = 6.8 Hz, C*H*$_3$^{i}Pr), 0.67 (dd, 6H, $^3J_{HP}$ = 13.0 Hz, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$^{i}Pr). ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = −0.93 (s, 1P, *P*i-Pr$_2$), −22.01 (s, 2P, *P*Ph$_2$). Elemental analysis: calcd. (%) for C$_{44}$H$_{49}$P$_3$Fe (726.64): C 72.73, H 6.80; found C 72.65, H 6.77.

General procedure for the catalytic reactions

In a Schlenk tube equipped with a stirring bar were introduced the aniline derivative (2 mmol, 1 equiv.), 1,2-dichloroarene (2 mmol, 1 equiv.), the complex [PdCl(η^3-C$_3$H$_5$)]$_2$ (0.02 mmol), **L5** (0.04 mmol), and *t*-BuONa (2.8 mmol, 1.4 equiv.). 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 the reactants were allowed to stir under reflux for 16 to 20 h. Then, the reaction mixture was analysed by GC-MS to determine the conversion of the reagents. At room temperature, 5 mL of diethyl ether was added and filtration using a pad of Celite® was done. The solvent was removed from the filtrate by heating the reaction vessel under vacuum and the residue was charged directly onto a silica gel column for flash chromatography.

2-Chlorodiphenylamine (3a)

From aniline (190 μL, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **3a** was obtained in 90% (366 mg) yield (pale yellow oil).

^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 7.29–7.24 (m, 2H), 7.22–7.18 (m, 1H), 7.09 (dt, *J* = 9.0 Hz, *J* = 3.0 Hz, 3H), 7.03 (dd, *J* = 9 Hz, *J* = 3.0 Hz, 1H), 6.96 (tt, *J* = 9.0 Hz, *J* = 3.0 Hz, 1H), 6.72 (qd, *J* = 9.0 Hz, *J* = 3.0 Hz, 1H), 6.03 (s, broad 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) = 141.5, 140.3, 129.7,

129.4(2C), 127.4, 122.7, 121.5, 120.4, 120.2(2C), 115.6. Elemental analysis: calcd (%) for $C_{12}H_{10}ClN$ (203.67): C 70.77, H 4.95; found C 71.04, H 4.82.

2-Chloro-2′-fluorodiphenylamine (3b)

From 2-fluoroaniline (200 μL, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **3b** was obtained in 98% (432 mg) yield (brown oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41–7.37 (td, J = 7.8 Hz, J = 1.2 Hz, 2H), 7.23 (t, 1H, J = 1.5 Hz, 1H), 7.17 (m, 1H), 7.14 (m, 1H), 7.10–6.95 (m, 2H), 6.90–6.84 (qd, J = 7.2 Hz, J = 1.8 Hz, 1H), 6.13 (broad s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 153.2 (d, J_{CF} = 242.0 Hz), 138.3, 128.8, 128.25 (d, J_{CF} = 187.0 Hz), 126.4, 123.3 (d, J_{CF} = 3.0 Hz), 121.6 (d, J_{CF} = 12.8 Hz), 120.19(2C), 120.2 (d, J_{CF} = 188.0 Hz), 115.2, 114.9 (d, J_{CF} = 19.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = −129.38. Elemental analysis: calcd (%) for $C_{12}H_9ClFN$ (221.66): C 65.02, H 4.09; found C 65.04, H 4.02.

2-Chloro-3′-fluorodiphenylamine (3c)

From 3-fluoroaniline (200 μL, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **3c** was obtained in 96% (437 mg) yield (brown oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H). 7.34 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.25–7.19 (m, 1H), 6.91–6.84 (m, 3H), 6.74–6.67 (tdd, J = 8.4 Hz, J = 2.4 Hz, J = 0.9 Hz, 1H), 6.45–6.36 (m, 1H), 6.13 (broad s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 162.6 (d, J_{CF} = 244 Hz), 142.6 (d, J_{CF} = 10.5 Hz), 138.1, 129.5 (d, J_{CF} = 8.25 Hz), 128.9, 126.5, 121.5 (d, J_{CF} = 12.8 Hz), 120.5, 115.9, 113.6 (d, J_{CF} = 3.0 Hz), 107.7 (d, J_{CF} = 21.0 Hz), 104.8 (d, J_{CF} = 25.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = −111.87. Elemental analysis: calcd (%) for $C_{12}H_9ClFN$ (221.66): C 65.02, H 4.09; found C 65.36, H 3.99. Best analysis obtained to date.

2-Chloro-4′-fluorodiphenylamine (3d)

From 4-fluoroaniline (200 μL, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol) **3d** was obtained in 99% (437 mg) yield (brown oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.25–7.22 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.04–6.99 (m, 2H), 6.97 (m, 1H), 6.94–6.89 (m, 3H), 6.66 (qd, J = 6.3 Hz, J = 2.4 Hz, 1H), 5.89 (broad s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.9 (d, J_{CF} = 240.0 Hz), 140.0, 136.2 (d, J_{CF} = 3.0 Hz), 128.6, 126.5, 122.2 (d, J_{CF} = 7.5 Hz, 2C), 119.8, 118.95, 115.1 (d, J_{CF} = 21.2 Hz, 2C), 113.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = −119.54. Elemental analysis: calcd (%) for $C_{12}H_9ClFN$ (221.66): C 65.02, H 4.09; found C 65.08, H 4.01.

2-Chloro-4′-methyldiphenylamine (3d′)

From *p*-toluidine (214 mg, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **3d** was formed in 62% yield (NMR). Spectroscopic data were identical to the ones previously reported.[12a]

(2-Chlorophenyl)pyridin-2-ylamine (5)

From 2-aminopyridine (189 mg, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **5** was obtained in 25% (102 mg) yield (yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.26 (dd, J = 6.0 Hz, J = 1.2 Hz, 1H), 8.07 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.55 (td, J = 7.8 Hz, J = 2.1 Hz, 1H), 7.40 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.25 (td, J = 8.7 Hz, J = 1.4 Hz, 1H), 6.94 (td, J = 7.8 Hz, J = 1.5 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.81 (dd, J = 7.2 Hz, J = 2.1 Hz, 1H), N*H* obscured. ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.9, 148.2, 137.8, 137.3, 129.5, 127.5, 123.2, 122.4, 119.7, 116.0, 110.1. Elemental analysis: calcd (%) for $C_{11}H_9ClN_2$ (204.67): C 64.56, H 4.43; found C 64.14, H 4.43. HR-mass (electrospray): found $[M + H]^+$ = 205.0537; calcd = 205.0527, δ = −4.8 ppm.

N-Methyl-2-chlorodiphenylamine (11)

From *N*-methylaniline (220 μL, 2 mmol) and 1,2-dichlorobenzene (230 μL, 2 mmol), **11** was obtained in 24% (134 mg) yield (yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (d, J = 6.0 Hz, 1H), 7.18 (t, J = 9.0 Hz, 2H), 6.94 (t, J = 9.0 Hz, 3H), 6.75 (t, J = 6.0 Hz, 1H), 6.59 (d, J = 6.0 Hz, 2H), 3.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.6, 145.4, 130.9, 129.2(2C), 128.8, 128.2, 121.3(2C), 117.8(2C), 113.5, 39.0. Spectroscopic data were in agreement with those reported in the literature;[25] however, the elemental analysis was unsatisfactory hypothetically due to some dehalogenation.

(2-Chloro-4-methyl)diphenylamine (3e)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3e** was obtained in 51% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.25 (d, J = 6.0 Hz, 2H), 7.22 (d, J = 1 Hz, 1H), 7.15 (d, J = 6.0 Hz, 1H), 7.09 (t, J = 9 Hz, 2H), 7.02 (d, J = 9 Hz, 1H), 6.55 (dd, J = 6.0 Hz, J = 1 Hz, 1H), 6.04 (broad s, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 141.7, 139.9, 130.9(2C), 129.5(2C), 129.0, 128.0, 121.4, 120.2(2C), 119.1.

(2-Chloro-5-methyl)diphenylamine (3e′)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3e′** was obtained in 17% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.25 (d, J = 6.0 Hz, 2H), 7.09 (t, J = 9.0 Hz, 2H), 7.02 (d, J = 9 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 5.96 (broad s, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 142.3(2), 137.5, 130.1, 129.5(2C), 122.5, 121.9, 120.2(2C), 118.6, 116.7.

(2-Chloro-3-methyl)diphenylamine (3f)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-3-methylbenzene (260 μL, 2 mmol), **3f** was obtained in 49% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.29 (m, 2H), 7.17–7.12 (m, 3H), 7.08–6.98 (m, 2H), 6.78–6.73 (m, 3H), 2.42

(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 141.85, 140.3, 137.1, 129.4, 127.9, 125.5, 121.9, 120.2, 115.2, 113.2, 20.7.

(2-Chloro-6-methyl)diphenylamine (3f′)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-3-methylbenzene (260 μL, 2 mmol), **3f′** was obtained in 17% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.29 (m, 2H), 7.17–7.12 (m, 2H), 7.08–6.98 (m, 2H), 6.78–6.73 (m, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 141.9, 140.3, 129.4, 128.9, 127.5, 126.9, 126.5, 122.5, 120.2, 113.2, 20.7.

(2-Chloro-4-methoxy)diphenylamine (3g)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-4-methoxybenzene (270 μL, 2 mmol), **3g** was obtained in 31% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33 (d, J = 9.0 Hz, 2H), 7.18 (m, 2H), 7.05 (m, 1H), 6.82 (d, J = 1.0 Hz, 1H), 6.76 (dd, J = 9.0 Hz, J = 1.0 Hz, 1H), 6.37 (dd, J = 9.0 Hz, J = 1.0 Hz), 6.09 (broad s, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.7, 141.2, 132.9, 130.6, 129.5, 123.9, 122.9, 120.6, 117.5, 113.6, 55.5.

(2-Chloro-5-methoxy)diphenylamine (3g′)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-4-methoxybenzene (270 μL, 2 mmol), **3g′** was obtained in 28% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33 (d, J = 9.0 Hz, 2H), 7.25 (m, 2H), 7.18 (m, 2H), 7.05 (m, 1H), 7.00 (d, J = 1.0 Hz, 1H), 6.09 (broad s, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.6, 141.2, 129.95, 129.5, 122.9, 120.6, 113.1, 105.6, 101.3, 55.7.

(2-Chloro-3-methoxy)diphenylamine (3h)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-3-methoxybenzene (356 mg, 2 mmol), **3h** was obtained in less than 5% yield (^{1}H NMR).

(2-Chloro-6-methoxy)diphenylamine (3h′)

From aniline (190 μL, 2 mmol) and 1,2-dichloro-3-methoxybenzene (356 μL, 2 mmol), **3h′** was obtained in 60% (281 mg) yield (orange solid).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32 (t, J = 7.5 Hz, 2H), 7.17 (d, J = 7.5 Hz, 2H), 7.1–7.03 (m, 2H), 6.90 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 6.47 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 6.19 (broad s, 1H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.8, 140.6, 140.5, 128.4(2C), 126.05, 121.7, 119.6(2C), 108.4, 106.9, 101.9, 55.2. $C_{13}H_{12}ClNO$ (233.69). HR-mass (electrospray): found $[M + Na]^+$ = 256.0499; calcd = 256.0500, δ = 0.3 ppm. Elemental analysis: calcd (%) for $C_{13}H_{12}ClNO$: C 66.81, H 5.18; found C 67.01, H 5.13.

(2-Chloro-4-methylphenyl)(2-methoxyphenyl)amine (3i)

From 2-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3i** was obtained in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.18 (m, 3*H*), 7.01–6.89 (m, 3*H*), 6.63 (d, J = 8.1 Hz, 1*H*), N*H* obscured, 3.89 (s, 3*H*), 2.27 (s, 3*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 149.0, 137.2, 131.0, 130.2, 130.1, 127.9, 120.8, 117.6, 117.0, 115.8, 110.7, 55.7, 20.4. The purification of this compound from its starting material (15%) and isomer was troublesome.

(2-Chloro-5-methylphenyl)(2-methoxyphenyl)amine (3i′)

From 2-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3i′** was obtained in 28% yield

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.18 (m, 3H), 7.01–6.89 (m, 3H), 6.63 (d, J = 8.1 Hz, 1H), N*H* obscured, 3.89 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 149.5, 139.4, 137.3, 129.4, 128.6, 121.6, 121.5, 120.7, 119.8, 110.9, 55.7, 21.3. The purification of this compound from its starting material (15%) and isomer was troublesome.

(2-Chloro-4-methylphenyl)(3-methoxyphenyl)amine (3j)

From 3-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3j** was obtained in 24% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31 (d, J = 8.1 Hz, 1H), 7.25–7.22 (m, 3H), 7.02–6.64 (m, 2H), 6.53 (dd, J = 8.1 Hz, J = 2.4 Hz, 1H), N*H* obscured, 3.79 (s, OC*H*$_3$), 2.28 (s, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 160.7, 143.7, 137.1, 131.0, 130.1, 129.3, 128.0, 118.9, 117.4, 111.3, 107.1, 104.5, 55.3, 20.4. The purification of this compound from its starting material (21%) and isomer was troublesome.

(2-Chloro-5-methylphenyl)(3-methoxyphenyl)amine (3j′)

From 3-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3j′** was obtained in 55% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.21–7.19 (d, J = 1.5 Hz, 1H), 7.14 (d, J = 1.2 Hz, 1H), 6.75 (dd, J = 8.1 Hz, J = 1.8 Hz, 2H), 6.71 (t, J = 2.4 Hz, 2H), 6.68–6.60 (m, 1H), N*H* obscured, 3.81 (s, OC*H*$_3$), 2.26 (s, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 160.7, 143.1, 139.6, 137.5, 130.1, 129.3, 121.6, 118.9, 116.9, 112.3, 107.7, 105.6, 55.3, 21.3. The purification of this compound from its starting material (21%) and isomer was troublesome.

(2-Chloro-4-methylphenyl)(4-methoxyphenyl)amine (3k)

From 4-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3k** was obtained in 25% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.20 (d, J = 8.4 Hz, 1H), 7.16 (m, 1H), 7.07–6.97 (m, 2H), 6.89 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 6.84–6.75 (m, 2H), 5.80 (broad s, N*H*), 3.71 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.9, 138.4, 133.8, 128.8, 129.0, 127.0, 123.5, 119.2, 113.7, 113.3, 54.5, 20.3. The purification of this compound from its starting material (29%) and isomer was troublesome.

(2-Chloro-5-methylphenyl)(4-methoxyphenyl)amine (3k′)

From 4-methoxyaniline (230 μL, 2 mmol) and 1,2-dichloro-4-methylbenzene (260 μL, 2 mmol), **3k′** was obtained in 46% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.09 (d, J = 8.1 Hz, 1H), 7.07–6.97 (m, 2H), 6.84–6.75 (m, 2H), 6.69 (s, 1H), 6.43 (d, J = 8.1 Hz, 1H), 5.70 (broad s, N*H*), 3.72 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 115.2, 140.7, 136.5, 133.1, 128.1, 123.5, 122.6, 118.9, 116.1, 113.7, 54.5, 19.2. The purification of this compound from its starting material (29%) and isomer was troublesome.

(2-Chloro-4-methoxyphenyl)(4-methylphenyl)amine (3l)

From 4-methylaniline (215 mg, 2 mmol) and 1,2-dichloro-4-methoxybenzene (270 μL, 2 mmol), **3l** was obtained in less than 10% yield (^{1}H NMR).

(2-Chloro-5-methoxyphenyl)(4-methylphenyl)amine (3l′)

From 4-methylaniline (215 mg, 2 mmol) and 1,2-dichloro-4-methoxybenzene (270 μL, 2 mmol), **3l′** was obtained in 50% yield in a mixture with 45% of the starting dichloride. Purification was troublesome.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.11 (q, J = 8.4 Hz, 4H), 6.76 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 6. 32 (d, J = 8.7 Hz, J = 2.7 Hz, 1H), N*H* obscured, 3.79 (s, OCH_3), 2.38 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.1, 140.7, 137.4. 131.8, 129.6, 128.9, 120.5, 114.6, 103.9, 99.5, 54.8, 19.7.

(2-Chloro-3-methoxyphenyl)(4-methylphenyl)amine (3m)

From 4-methylaniline (217 mg, 2 mmol) and 1,2-dichloro-3-methoxybenzene (355 mg, 2 mmol), **3m** was obtained in 67% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.20–7.00 (m, 2H), 6.83 (dd, J = 8.1 Hz, J = 1.44 Hz, 2H), 6.79 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.43 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H). 5.29 (s, N*H*), 3.91 (s, OCH_3), 2.33 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.4, 142.4, 138.7, 132.8, 129.9, 122.3, 122.2, 110.0, 107.3, 102.4, 56.5, 20.8.

(2-Chloro-6-methoxyphenyl)(4-methylphenyl)amine (3m′)

From 4-methylaniline (217 mg, 2 mmol) and 1,2-dichloro-3-methoxybenzene (355 mg, 2 mmol), **3m′** was obtained in 13% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.20–7.00 (m, 9.2H), 6.83 (dd, J = 8.1 Hz, J = 1.44 Hz, 2H), 6.79 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H), 6.63 (m, J = 8.5 Hz, 1H), 6.43 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 5.29 (s, NH), 3.80 (s, OCH_3), 2.27 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.8, 138.7, 133.9, 129.3, 127.4, 127.1, 124.4, 121.7, 116.2, 56.2, 20.8.

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