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Reversal of aryl bromide reactivity in Pd-catalysed aryl amination reactions promoted by a hemilabile aminophosphine ligand

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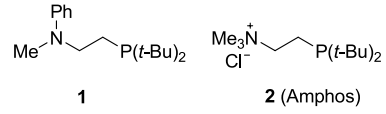
Abstract—Incorporation of a hemilabile amino group with a bulky, electron-rich phosphorus ligand led to a reversal in the order of aryl bromide reactivity in Pd-catalysed aryl amination reactions.

1. Introduction

Electron-rich, sterically bulky alkylphosphines constitute the majority of ligands that promote palladium-catalysed cross-coupling reactions under mild reaction conditions. The remarkable reactivity has been attributed to the ability of these bulky ligands to provide highly coordinatively unsaturated, nucleophilic palladium catalytic precursors.[1]

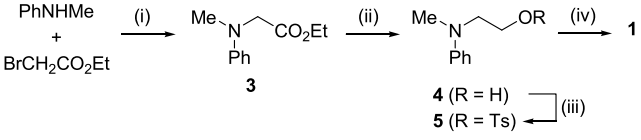
As part of our continued effort to develop nitrogen–phosphorus hybrid ligands for transition-metal mediated catalysis,[2] the aminophosphine ligand **1** was synthesised and its catalytic activity examined. We are particularly interested in exploring potential beneficial effect(s) of introducing a hemilabile nitrogen donor on catalyst activity and/or stability. Combining a bulky di-*tert*-butylphosphine moiety with a hemilabile tertiary amine donor, it is structurally similar to the Amphos ligand (**2**), which has been found to promote Suzuki, Sonogashira, and Heck couplings of aryl bromides in aqueous solvents.[3] The quaternarised amino functionality is not expected to coordinate to the palladium metal centre, but improves the water-solubility of the palladium catalysts, which may be recovered and recycled without any lost of activity (Fig. 1).

The aminophosphine **1** can be prepared expediently in four steps (Scheme 1): *N*-Methylaniline was alkylated with bromoethylacetate to give the amino ester **3**. This was reduced and the resultant amino alcohol was transformed into amino tosylate **4**. Finally, a nucleophilic substitution by di-*tert*-butylphosphide furnished the product **1** as a dense oil. To facilitate handling, the ligand was precipitated and stored as the white crystalline HCl salt, which is remarkably stable to air and moisture—a solution of **1**·HCl may be left exposed to air at room temperature for at least 24 h without any significant oxidation (^{31}P NMR spectroscopy).



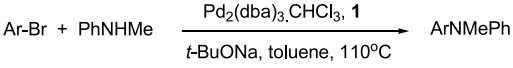
1 **2** (Amphos)

Figure 1. Sterically bulky aminophosphine ligands.



Scheme 1. Preparation of ligand **1**. (i) Na_2CO_3, EtOH; (ii) $LiAlH_4$, THF; (iii) TsCl, pyridine; (iv) (a) *t*-Bu_2PH, *t*-BuLi.

Ligand **1** was subsequently employed in a number of palladium-catalysed reactions, including the amination of aryl bromides (Scheme 2), where the reaction between the sterically bulky *N*-methylaniline with a number of aryl bromides (4-bromoacetophenone, 4-bromobenzonitrile,



Scheme 2. Pd-catalysed aryl amination reaction.

Keywords: Palladium catalysis; PN ligands; Aryl amination; Aryl bromides.
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bromobenzene and 4-bromoanisole) was examined. Despite our initial expectations, no reaction was observed at ambient temperature. This could be due to the coordination of the nitrogen donor group and/or the amine substrate, which suppresses the formation of the reactive coordinatively unsaturated Pd(0) species for the initial oxidative addition step.[†]

As an elevated reaction temperature was necessary to enable catalytic turnover, 1,1′-bis(diphenylphosphino)ferrocene (dppf), previously reported to be an effective ligand for the aryl amination of primary amines,[4] was employed as a comparison, to gauge the catalytic efficiency of ligand **1** and to discount the involvement of catalytic active palladium colloids (Table 1).[5] Under the adopted reaction conditions, dppf is an ineffective ligand for the coupling of this secondary amine. At 1 mol% catalytic loading, less than 12% of products were obtained in 21 h, irrespective of the electronic nature of the aryl halide ligand (Table 1, entries 1–4). In contrast, ligand **1** gave better yields of products (entries 5–12).

Table 1. Pd-catalysed aryl amination reactions (Scheme 2)[a]

Entry	Ar-Br	Ligand	Pd:L[b]	Yield %[c]
1	4-NCC_6H_4Br	dppf	1:1.1	11
2	4-$MeOCC_6H_4Br$	dppf	1:1.1	—
3	PhBr	dppf	1:1.1	7
4	4-$MeOC_6H_4Br$	dppf	1:1.1	9
5	4-NCC_6H_4Br	1	1:1.1	36
6	4-NCC_6H_4Br	1	1:0.8	34
7	4-$MeOCC_6H_4Br$	1	1:1.1	29
8	4-$MeOCC_6H_4Br$	1	1:0.8	21
9	PhBr	1	1:1.1	80
10	PhBr	1	1:0.8	66
11	4-$MeOC_6H_4Br$	1	1:1.1	83
12	4-$MeOC_6H_4Br$	1	1:0.8	93

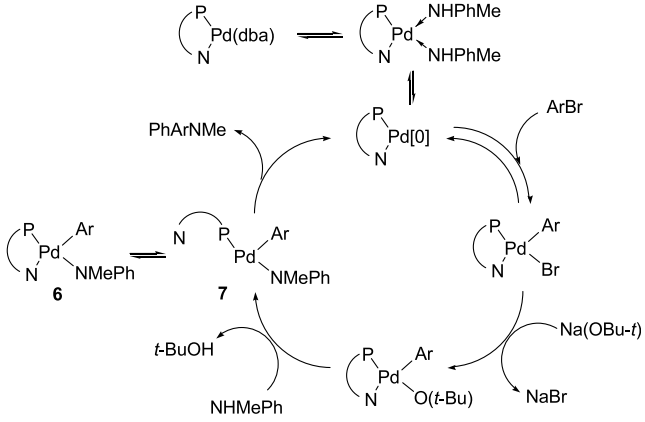
[a] Reaction conditions: $Pd_2(dba)_3 \cdot CHCl_3$, ligand, aryl halide (1 equiv), *N*-methylaniline (1 equiv) and sodium *tert*-butoxide (1.5 equiv) in toluene at 110 °C, 21 h (reaction time unoptimised).
[b] Metal-to-ligand ratio (mol%).
[c] Isolated yield after column chromatography. Duplicated to within 5%.

It is a well-established fact that electron-deficient aryl bromides are 'privileged' substrates in palladium catalysis, as they undergo cross-coupling reactions much more readily than electron-rich aryl bromides. In particular, 4-bromoacetophenone demonstrably undergo cross-coupling reactions with exceptionally high TON's even in the absence of any added ligand, thus has been discounted as a useful benchmark for the evaluation of new catalysts.[6] In light of this, we were surprised to find that ligand **1** imposes an unexpected pattern of reactivity in the aryl amination reactions: electron-deficient substrates, 4-bromoacetophenone and 4-bromobenzonitrile, gave very low yield of products under these reaction conditions (<40%, entries 5 and 7). Conversely, electronically-neutral (bromobenzene) and the electron-rich (4-bromoanisole) aryl bromide substrates gave much higher yields under identical conditions (>80%, entries 9 and 11).

As the yields are equally low for the electron-deficient substrates, complexation of the nitrile moiety to the metal centre is not regarded as a major factor under these reaction conditions. Crucially, in both cases, recovered aryl bromide substrates accounted for the mass balance, that is the low yields were not due to competitive side reactions (e.g., dehalogenation).

These observations clearly contradict the established trends of palladium-catalysed aryl amination reactions, where electron-withdrawing substituents on the aryl moiety enhances the rate of turnover in both the bond-breaking (oxidative addition of aryl halide to the Pd precursor) and bond-making (reductive elimination of arylpalladium amido intermediate) steps.[7]

In our earlier work,[2] we have demonstrated that the hemilability of nitrogen–phosphorus ligands are highly sensitive to the electronic nature of the palladium metal centre. Furthermore, in a recent study by Hartwig et al., 3-coordinate [(L)Pd(Ar)(NAr'_2)] complexes were reported to undergo much faster (irreversible) reductive elimination than their corresponding 4-coordinate [$(L)_2$Pd(Ar)(NAr'_2)] complexes in the C–N bond forming step.[8] Hence, a slight modification of the conventional aryl amination catalytic cycle[9] is proposed, to accommodate the hemilability of the PN ligand (Scheme 3). Following the initial oxidative addition reaction, a series of ligand exchanges occur, leading to the formation of 3- and/or 4-coordinated arylpalladium amido complexes (**6** and **7**), depending on the coordination mode of the PN ligand. In the presence of an electron-rich aryl moiety, the electron density and Lewis acidity of the palladium(II) metal centre is enhanced, which discourages the coordination of the π-basic nitrogen donor. This favours the formation of the complex **7**, which undergoes faster C–N bond formation to furnish the product.



Scheme 3. Proposed catalytic cycle involving ligand **1**.

Further credence to this theory is provided by the effect of the metal-to-ligand ratio. Lowering the ratio have very little effect on the reactions involving electron-deficient aryl bromides (Table 1, entries 5 vs 6, and 7 vs 8), but led to a marked improvement in the reaction of 4-bromoanisole (entries 11 and 12). This fits with the conjecture that excess

[†] Indeed, in the absence of the amine substrate, ligand **1** is able to promote slow catalytic turnover in the Suzuki–Miyaura cross-coupling between aryl bromides and aryl boronic acids at 25 °C. Compared to the catalytic activity of Amphos **2**, which catalyses the C–C bond forming reactions in 1–2 h,[3] the involvement of the hemilabile amino group in the catalytic cycle is also clearly implicated.

ligand could lead to the formation of a 4-coordinate [L_2Pd(Ar)(NMePh)] complex, thus inhibiting the formation of the more reactive metal complex. Interestingly, lowering the *M*:*L* ratio led to a decrease in yield for the reaction involving the bromobenzene substrate (entries 9 and 10). The reason for this observation is unclear at this stage—the presence of a slight excess of the ligand could have improved the catalyst's stability, as was observed for Amphos ligands. However, the operation of a competitive side reaction cannot be ruled out entirely, as it is difficult to quantify formation of the dehalogenated product (benzene).

In summary, the incorporation of a hemilabile amino functionality with sterically bulky, electron rich di-*tert*-butylphosphine aminophosphine led to a very unusual pattern of reactivity in the palladium-catalysed aryl amination of aryl halides, contradicting the conventional notion of 'activated' and 'unactivated' aryl bromides in cross-coupling reactions. The serendipitous discovery will be exploited in the design of ligands for chemoselective catalysis. Further studies on the coordination and catalytic chemistry of this and related aminophosphine ligands will be conducted in our future work.

2. Experimental

2.1. General

THF was freshly distilled under N_2 from sodium benzophenone. Toluene, CH_2Cl_2 and *n*-hexane were freshly distilled from CaH_2 also under N_2. Triethylamine was distilled under Ar from CaH_2 and stored over KOH pellets. Commercially available chemicals were purchased from Aldrich, Avocado, BDH, Fluka, Lancaster or Strem chemical companies, which were used as received, unless otherwise stated. Tris-(dibenzylideneacetone)dipalladium-(chloroform), $Pd_2(dba)_3\cdot(CHCl_3)$, was prepared by established procedure.[10] Air- or moisture- sensitive reactions were carried out under inert atmosphere (N_2 or Ar) using standard Schlenk line techniques. Glassware was oven-dried overnight. Melting points were determined on electrothermal Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using Bruker AM 360, AVANCE 400 and 500 spectrometers in $CDCl_3$. ^{1}H NMR and ^{13}C NMR spectra were referenced to tetramethylsilane (TMS) while ^{31}P NMR spectra were referenced to H_3PO_4 (external standard). Chemical shifts are recorded in parts per million (δ, ppm) downfield to TMS or H_3PO_4. Coupling constants are given in Hertz (*J* Hz). The following abbreviations are used to describe multiplicity: s-singlet, t-doublet, t-triplet, q-quartet, m-multiplet, dd-double doublet, dt-double triplet, td-triple doublet. Mass spectra (MS) were recorded by the mass spectrometry service within the university of London's intercollegiate research services (ULIRS) or EPSRC MS services at university of swansea, Wales. Elemental analyses were carried out by elemental analysis service, London metropolitan university.

2.1.1. (Methyl-phenyl-amino)-acetic acid ethyl ester, 3. Ethyl bromoacetate (6.65 mL, 60 mmol, 1.1 equiv) was added slowly at room temperature to a solution of *N*-methylaniline (5.9 mL, 54 mmol, 1.0 equiv) in EtOH (100 mL). The reaction mixture was stirred at room temperature for 30 min before Na_2CO_3 (19.4 g, 183 mmol, 1.5 equiv) was added and refluxed overnight. After cooling to room temperature, the solution was concentrated by evaporation and diluted with 30 mL of Et_2O. The precipitated salts were removed by filtration through Celite, which were thoroughly rinsed with Et_2O and CH_2Cl_2. The filtrate was acidified by the addition of 1 M aqueous HCl (pH=1). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$ and evaporated to furnish a dark oil. The crude product was purified by distillation under reduced pressure to yield the ester was obtained as a pale yellow oil (9.73 g, 93%). Bp: 90 °C, 1.0 mmHg (lit.[11] 90–92 °C, 0.2 mmHg); ν (thin film)/cm^{-1} 1742 (C=O); δ_H (360 MHz, $CDCl_3$) 1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 3.13 (3H, s, NCH_3), 4.12 (2H, s, NCH_2), 4.24 (2H, q, J=7.1 Hz, CH_2CH_3), 6.79 (2H, d, J=8.7 Hz, H_{ortho}), 6.85 (1H, t, J=7.4 Hz, H_{para}), 7.33 (2H, dd, J=7.4, 8.7 Hz, H_{meta}); δ_C (90.5 MHz, $CDCl_3$) 14.7 (s, CH_2CH_3), 39.9 (s, NCH_3), 54.9 (s, NCH_2), 61.2 (s, CH_2CH_3), 112.7 (s, C_{ortho}), 117.7 (s, C_{para}), 129.6 (s, C_{meta}), 149.4 (s, C_{ipso}), 171.4 (s, CO).

2.1.2. *N*-(2-Hydroxyethyl)-*N*-methyl-aniline 4.[12] In a two-necked round bottom flask fitted with a condenser, lithium aluminium hydride (2.9 g, 75 mmol, 2.0 equiv) was suspended in 30 mL of freshly distilled THF. The reaction mixture was cooled down to 0 °C, and the ester **3** (7.3 g, 37 mmol, 1.0 equiv) was added dropwise. The solution was stirred at room temperature for 1 h before being refluxed for 4 h. After cooling to 0 °C, the excess reducing agent was destroyed carefully by the alternate addition of H_2O and 15% aqueous NaCl. The resultant white solid was removed by filtration through a pad of Celite, which was washed repeatedly with Et_2O. The filtrate was separated and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to yield the amino alcohol as a pale yellow liquid, which was employed in the next step without any further purification (5.2 g, 92%); δ_H (360 MHz, $CDCl_3$) 2.07 (1H, br s, OH), 2.85 (3H, s, CH_3), 3.35 (2H, t, J=5.8 Hz, NCH_2), 3.68 (2H, t, J=5.8 Hz, CH_2O), 6.65 (1H, t, J=7.2 Hz, H_{para}), 6.70 (2H, d, J=8.3 Hz, H_{ortho}), 7.15 (2H, dd, J=7.2, 8.3 Hz, H_{meta}); δ_C (90.5 MHz, $CDCl_3$) 39.2 (s, CH_3), 55.8 (s, NCH_2), 60.4 (s, CH_2O), 113.4 (s, C_{ortho}), 117.6 (s, C_{para}), 129.6 (s, C_{meta}), 150.4 (s, C_{ipso}).

2.1.3. *N*-(2-tosylethyl)-*N*-methyl-aniline, 5.[13] *p*-Toluenesulfonyl chloride (4.5 g, 23 mmol, 1.4 equiv) was added slowly to 11 mL of ice-cooled pyridine. The resulting orange solution was allowed to warm to room temperature. After 30 min, the reaction mixture was cooled to −10 °C (ice-acetone bath), whereupon **4** (2.4 g, 16 mmol, 1.0 equiv) was added portionwise over 30 min. The mixture was allowed to warm to room temperature and stirred for 2 h. The resultant slurry was poured into an ice-water (40 mL), stirred for 30 min and CH_2Cl_2 (30 mL) were then added. The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were treated with 4 M aqueous HCl until the pH was acidic

(4–5, pH paper). The solution was washed with brine (30 mL), saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and evaporated to furnish a yellow oil (3.7 g, 75%); δ_H (360 MHz, $CDCl_3$) 2.31 (3H, s, CH_3), 2.77 (3H, s, NCH_3), 3.49 (2H, t, $J=6.1$ Hz, NCH_2), 4.06 (2H, t, $J=6.1$ Hz, CH_2O), 6.47 (2H, d, $J=8.2$ Hz, tol), 6.60 (1H, t, $J=7.3$ Hz, Ph_{para}), 7.10 (2H, dd, $J=7.3$, 8.6 Hz, Ph_{meta}), 7.18 (2H, d, $J=8.2$ Hz, tol), 7.61 (2H, d, $J=8.6$ Hz, Ph_{ortho}); δ_C (90.5 MHz, $CDCl_3$) 22.0 (s, CH_3), 39.3 (s, NCH_3), 51.6 (s, NCH_2), 67.5 (s, CH_2O), 112.5 (s, Ph_{ortho}), 117.3 (s, Ph_{para}), 128.3 (s, tol), 129.6 (s, Ph_{meta}), 130.2 (s, tol), 133.1 (s, tol), 145.3 (s, Ph_{ipso}), 150.2 (s, tol).

2.1.4. [2-Di-(*tert*-butyl)-phosphinoethyl]-*N*-methylaniline, 1. Di-*tert*-butylphosphine (1.0 g, 6.8 mmol, 1.1 equiv) was placed in an oven dried Schlenk tube with 10 mL of degassed Et_2O. The solution was cooled down at 0 °C and a solution of *tert*-butyllithium (1.5 M in pentane, 5.5 mL, 1.3 equiv) was added dropwise. The reaction was allowed to warm to room temperature. After 1 h, it was cooled to 0 °C and 1.0 equiv of the tosylate **5** (1.9 g, 6.2 mmol) was added slowly. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for a further 3 h, whereupon the colour changed from yellow to orange (completion of the reaction was monitored by recording the ^{31}P NMR spectrum of the reaction aliquot). The reaction mixture was quenched by the addition of 2.0 mL of freshly distilled MeOH. The solvent was then removed in vacuo. Distilled toluene (20 mL) was added, stirred and the resulting solution was filtered into a pre-weighed Schlenk tube. The solvent was evaporated under vacuum to give a pale oil. Ten cubic centimetres of degassed petroleum ether were added, the solution was stirred at room temperature and evaporated to furnish an oily solid. In order to facilitate the handling of this ligand, the corresponding ammonium salt was formed, achieved by dissolving the oily solid in degassed Et_2O, followed by addition of a few drops of degassed concd. HCl. Upon cooling, the ammonium salt precipitated, which was collected and dried in vacuo. Yield: 91% (1.39 g, pale dense oil). Although the crystalline ligand may be handled in air without any problems, it is stored under an inert atmosphere. Mp (HCl salt) 160–162 °C; Found: C, 72.99; H, 10.73; N, 5.09. $C_{17}H_{30}NP$ requires C, 73.12; H, 10.75; N, 5.02%; δ_H (360 MHz, $CDCl_3$) 1.06 (18H, d, $^3J_{PH}=11.2$ Hz, CH_3), 1.53 (2H, td, $^2J_{PH}=4.8$ Hz and $^3J_{HH}=9.0$ Hz, NCH_2CH_2P), 2.86 (3H, s, CH_3), 3.43 (2H, td, $^3J_{PH}=4.3$ Hz and $^3J_{HH}=9.0$ Hz, NCH_2CH_2P), 6.60 (2H, d, $J=8.6$ Hz, *Ph*), 7.07 (1H, d, $J=7.4$ Hz, *Ph*), 7.14 (2H, dd, $J=7.4$, 8.6 Hz, *Ph*); δ_C (90.5 MHz, $CDCl_3$) 18.3 (d, $^1J_{PC}=23.0$ Hz, CH_2P), 30.1 (d, $^2J_{PC}=13.5$ Hz, CH_3), 31.7 (d, $^1J_{PC}=19.0$ Hz, CMe_3), 38.6 (s, CH_3), 54.3 (d, $^2J_{PC}=39.3$ Hz, NCH_2), 112.8 (s, C_{meta}), 116.6 (s, C_{para}), 129.7 (s, C_{ortho}), 149.0 (s, C_{ipso}); δ_P (146 MHz, $CDCl_3$) +25.7; *m/z* (FAB) 280.2 (MH^+), 145 ($M^+ - C_9H_{12}N$), 134 ($C_9H_{12}N^+$), 77 ($C_6H_5^+$), 57 ($C_4H_9^+$).

2.2. Pd-catalysed aryl amination reaction

Sodium *tert*-butoxide (387 mg, 4 mmol, 1.5 equiv) and a magnetic stirrer bar were introduced into a Schlenk tube, which was repeatedly purged and filled with dry N_2. *N*-Methylaniline (286 mg, 2.67 mmol, 1 equiv), the relevant aryl bromide (1 equiv) and toluene (1 mL) were added to generate a reaction mixture. Meanwhile, $Pd_2(dba)_3 \cdot CHCl_3$ (13.8 mg, 0.013 mmol, 0.5 mol%), ligand **1**·HCl (9.5 mg, 0.030 mmol, 1.1 equiv) and sodium *tert*-butoxide (0.032 mmol) were weighed into a separate vessel and dissolved in warm toluene (1 mL). The solution of the catalyst precursor was transferred via syringe into the reaction vessel, which was heated at 100 °C for 21 h. After cooling, the reaction mixture was diluted with EtOAc (20 mL) and filtered to remove any insoluble material. The solvents were evaporated, and the residue was subjected to column chromatography (flash silica gel) using ethyl acetate/hexane as eluent.

2.2.1. *N*-(4-acetophenone)-*N*-methylaniline.[14] δ_H (360 MHz, $CDCl_3$) 7.83 (2H, d, $J=9.0$ Hz, $H_{meta'}$), 7.44 (2H, dd, $J=8.4$, 7.3 Hz, H_{meta}), 7.25 (1H, t, $J=8.4$ Hz, H_{para}), 7.24 (2H, d, $J=7.3$ Hz, H_{ortho}), 6.77 (2H, d, $J=9.0$ Hz, $H_{ortho'}$), 3.40 (3H, s, NCH_3), 2.53 (3H, s, $COCH_3$).

2.2.2. *N*-(4-Cyanophenyl)-*N*-methylaniline.[15] δ_H (360 MHz, $CDCl_3$) 7.40–7.30 (4H, m, H_{meta}), 7.18 (1H, t, $J=7.4$ Hz, H_{para}), 7.13 (2H, d, $J=7.0$ Hz, H_{ortho}), 6.64 (2H, d, $J=11.0$ Hz, H_{ortho}), 3.27 (3H, s, NCH_3).

2.2.3. Methyl diphenylamine.[16] δ_H (360 MHz, $CDCl_3$) 7.20 (4H, dd, $J=8.5$, 7.3 Hz, H_{meta}), 6.90 (4H, d, $J=8.5$ Hz, H_{ortho}), 6.70 (2H, t, $J=7.3$ Hz, H_{para}), 3.20 (3H, s, NCH_3).

2.2.4. *N*-(4-Methoxyphenyl)-*N*-methylaniline.[17] δ_H (360 MHz, $CDCl_3$) 7.24 (2H, dd, $J=9.0$, 7.4 Hz, H_{meta}), 7.15 (2H, d, $J=9.0$ Hz, $H_{meta'}$), 6.95 (2H, d, $J=9.0$ Hz, $H_{ortho'}$), 6.87 (2H, d, $J=9.0$ Hz, H_{ortho}), 6.85 (1H, t, $J=7.4$ Hz, H_{para}), 3.70 (3H, s, OCH_3), 3.15 (3H, s, NCH_3).

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