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Easily Accessible Benzamide-Derived P,O Ligands (Bphos) for Palladium-Catalyzed Carbon–Nitrogen Bond-Forming Reactions

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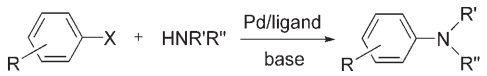
Abstract: Easily accessible benzamide-derived hemilabile phosphine ligands were efficiently prepared through *ortho*-directed lithiation of the corresponding *N,N*-diethylbenzamide followed by quenching with chlorodialkylphosphines. These structurally simple hemilabile ligands were found to be highly effective in palladium-catalyzed amination of aryl and heteroaryl chlorides. Various sterically congested and functionalized aryl halide substrates were compatible in these reaction conditions. By using optimized reaction conditions, remarkable catalyst productivity (total turnover number up to 8400) was obtained.

Keywords: amination · benzamide · catalysis · palladium · phosphines

Introduction

Transition-metal-catalyzed carbon–nitrogen bond-forming reactions have evolved into a highly versatile and synthetically attractive transformation in targeting pharmaceutically interesting intermediates.[1] Since the first general and efficient procedures were discovered,[2] efforts towards increasing substrate scope and efficiency have been made. This so-called Buchwald–Hartwig amination reaction[3] occurs in the presence of palladium catalysts with various phosphine ligands and an excess of base (Scheme 1).[4]



Scheme 1. Palladium-catalyzed amination reactions.

Of the different substrates that are readily available, the economically attractive aryl chlorides require a special and unique catalyst design for successful coupling, unlike aryl bromides and iodides.[5] This is a consequence of the bond energy, as that of Ph–Cl (402 kJ mol^{-1}) is much higher than for both Ph–Br (339 kJ mol^{-1}) and Ph–I (272 kJ mol^{-1}) at 298 K.[6] Recently developed ligands that are both electron-rich and sterically congested at the phosphorus donor atom show high activity in assisting the palladium-catalyzed amination of various aryl halides, especially the unreactive aryl chloride substrates (Figure 1).[7] With regard to catalyst development, tri-*o*-tolylphosphine was originially used as the ligand, but this arylphosphine gave poor results with primary amines and did not work with nonactivated aryl chlorides.[8]

Substantial improvements have been made from the late 1990s to 2005 in methods for carbon–carbon and carbon–heteroatom bond formation (Figure 1).[7,9] The state-of-the-art ligands are mainly monodentate phosphines.[10] A number of generally accepted reports state that an efficient metal complex for catalysis is often coordinatively unsaturated, whereas a stable metal complex, which is usually coordinatively saturated, shows less catalytic activity.[11] We were attracted by the characteristic property of the hard and soft hemilabile coordination of amides,[12,13] which can potentially provide a dynamic "on and off" chelating effect for the metal complex during catalysis (Figure 2). However, phosphine ligands with hemilabile groups have seldom been studied in Pd-catalyzed C–N bond-forming reactions.[14] Therefore, there remains room for the exploration of simple and highly efficient supporting ligands.

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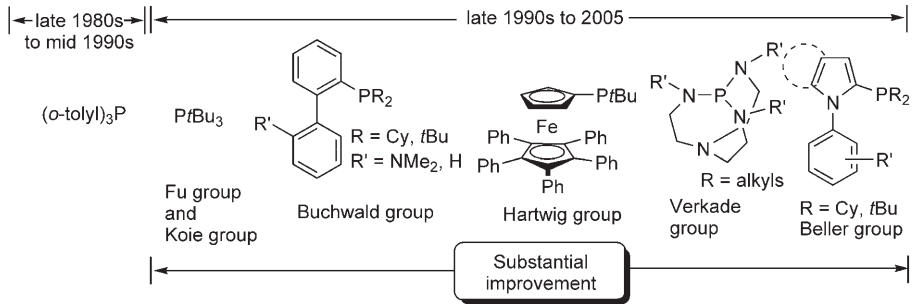


Figure 1. Recent development of highly reactive monodentate phosphine ligands. Cy = cyclohexyl.

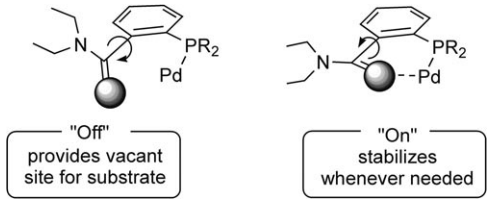
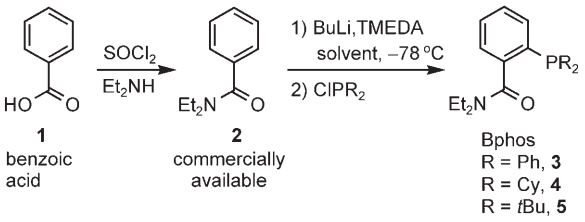


Figure 2. Concept of a potentially hemilabile Bphos ligand.

Based on these reasons, we explored a class of hemilabile phosphine ligands that enjoy potential beneficial features in stabilizing the complex while avoiding the problems of coordinative saturation for Pd-catalyzed coupling reactions. Herein, we report a full account of the efficient single-step ligand synthesis and the application of these easily accessible benzamide-derived P,O-type ligands for palladium-catalyzed amination of aryl and heteroaryl chlorides.[15]

Results and Discussion

Commercially available *N,N*-diethylbenzamide (**2**) was chosen to be the starting material for the single-step preparation of P,O-type ligands (Scheme 2). Alternatively, this starting material could be easily obtained from inexpensive benzoic acid (**1**) or benzoyl chloride and dialkylamines in quantitative yield. Notably, the ligand scaffold can be potentially fine-tuned by using different readily available substituted benzoic acid derivatives. This characteristic feature is of significance for obtaining a diverse ligand family in tackling a broad spectrum of substrates (Figure 3).



Scheme 2. Simple synthesis of Bphos ligands. Bphos = benzamide-derived phosphine, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

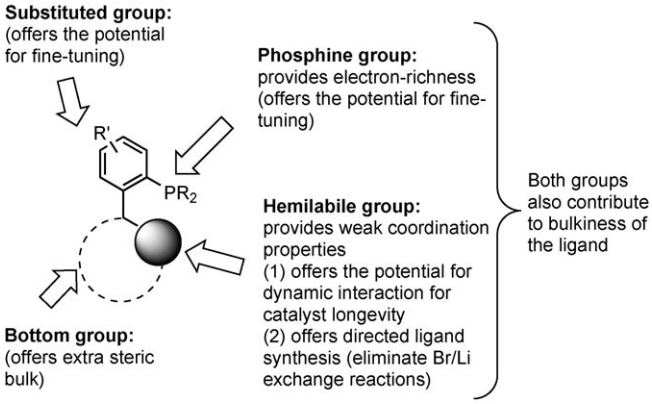


Figure 3. Ligand design and development of diversity.

The *ortho*-directing lithiation protocol, which was extensively studied by Beak, Snieckus, and co-workers,[16,17] was used as the key step in the synthesis of Bphos ligands (Scheme 2).[18] This straightforward synthetic route avoids the metal/halogen exchange (from ArBr or ArI) reactions. The directed *ortho*-metallation process of benzamide **2** was particularly optimized for the preparation of ligand **3** (Table 1 and Scheme 2). We examined the lithiation protocol as a function of reaction solvent, organolithium, complexing agent, temperature, and the order of addition. The best conditions found for directed metallation of **2** were the slow addition of amide in freshly distilled THF to a slight excess of *sec*-BuLi/TMEDA complex in THF at −78 °C (Table 1, entry 1). A significant amount of the side product, *N,N*-diethyl-*o*-benzoylbenzamide, was obtained when the order of addition was reversed.[19] The complexing agent TMEDA is necessary for this process. We observed a partial conversion of **2** into the *ortho*-benzoyl product in the absence of TMEDA.[20] At-

Table 1. Optimization of the synthesis of ligand **3** by the directed *ortho*-metallation protocol.[a]

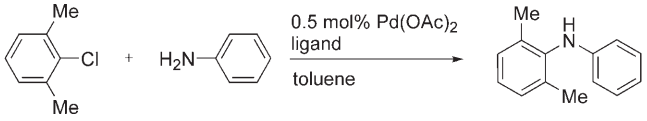
Entry	Base	Complexing agent	Solvent	Yield [%][b]
1	*sec*-BuLi	TMEDA	THF	64[d]
2[c]	*sec*-BuLi	TMEDA	THF	15
3	*sec*-BuLi	none	THF	9
4	*n*BuLi	TMEDA	THF	trace
5	*sec*-BuLi	TMEDA	diethyl ether	20

[a] *N,N*-diethylbenzamide (**2**) (1.0 mmol) was used as the substrate. At −78 °C, the amide in THF was added to the precomplexed organolithium reagent in THF (stirred for 15–30 min), followed by quenching with chlorodiphenylphosphine. [b] Yield of isolated product. [c] Order of addition was reversed, that is, *sec*-BuLi/TMEDA was added to the solution of amide. [d] Average of more than three independent runs.

tempted *ortho*-deprotonation of **2** with *n*BuLi provided a large quantity of valerophenone (Table 1, entry 4). This ketone presumably resulted from the nucleophilic addition of *n*BuLi to **2**.[21] When the solvent was changed to diethyl ether, the side reaction, nucleophilic attack, became dominant. Under the optimal conditions, other Bphos analogues were prepared.

One of the challenging amination reactions is the coupling of sterically hindered 2,6-disubstituted aryl chlorides with amines. To test the effectiveness of these Bphos ligands, we used the sterically hindered 2-chloro-*m*-xylene and aniline as prototypical substrates (Table 2). Initially, Bphos ligands

Table 2. Investigation of phosphine ligands in Pd-catalyzed amination of aryl chloride.[a]



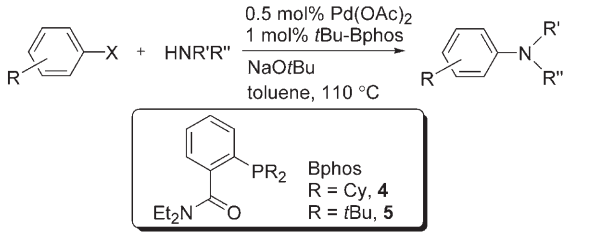
Entry	Ligand	Conv. [%]	Yield [%][b]
1	none	0	0
2	Ph_3P	2	trace
3	binap	6	3
4	Ph-Bphos **3**	9	4
5	Cy-Bphos **4**	69	68
6	*t*Bu-Bphos **5**	98	97
7	*o*-(*t*Bu_2P)-biphenyl	98	98
8	*t*Bu_3P	99	91
9	*n*$BuPAd_2$	95	88

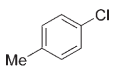
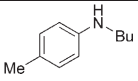
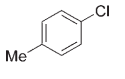
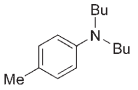
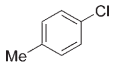
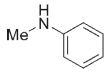
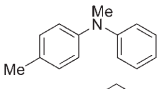
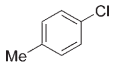
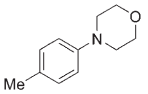
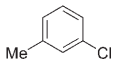
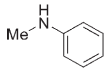
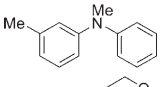
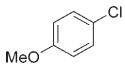
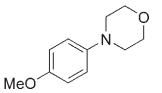
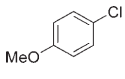
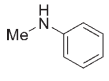
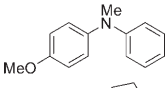
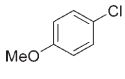
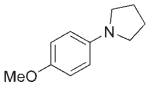
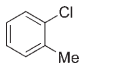
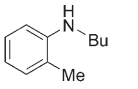
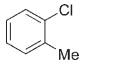
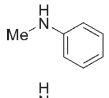
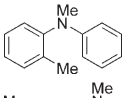
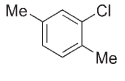
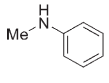
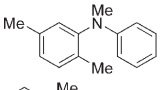
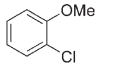
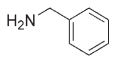
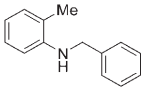
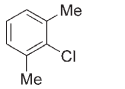
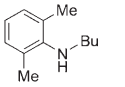
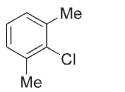
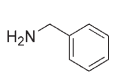
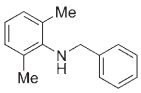
[a] ArCl (1.0 mmol), aniline (1.2 mmol), NaO*t*Bu (1.4 mmol), $Pd(OAc)_2$ (0.5 mol%), phosphine ligand (1.0 mol%) (Pd/P atom = 1:2), toluene (2.0 mL), 20 h, 110–115 °C. [b] Average of two runs, determined by calibrated GC analysis with dodecane as internal standard. Ad = adamantyl, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

3–**5** and other commercially available phosphine ligands were tested in this catalytic process. The control experiment revealed that a phosphine ligand is necessary to trigger the amination reaction (Table 2, entry 1). Triphenylphosphine showed nearly no reactivity in this catalysis. The bidentate binap ligand,[22] which displayed excellent ability in assisting Pd-catalyzed amination of aryl bromides and triflates,[23] was found to be inactive in this coupling reaction. Bphos ligand **3** with a diphenylphosphanyl moiety gave a poor conversion of aryl chloride.[24] When electron-rich dicyclohexylphosphanyl derivative **4** was used, better conversion and yields were obtained (Table 2, entry 5). Upon using the more sterically bulky ligand **5**, both excellent conversion and yield were achieved. Presumably, the steric bulk of the benzamide skeleton, the dialkylphosphanyl group, and the hemilabile amide carbonyl oxygen atom jointly contributed to the high activity. We have demonstrated that these Bphos ligands work at least as well as "state-of-the-art" ligands such as *o*-(*t*Bu)$_2$biphenyl,[25] *t*Bu_3P,[26] and *n*$BuPAd_2$ (cataCXium A)[27] in sterically hindered chloroarene amination test reactions (Table 2, entries 5–9).

The general usefulness of the Bphos ligands is shown in Tables 3, 4, and 5. The reactions of a variety of aryl and het-

Table 3. Palladium–Bphos-catalyzed amination of a variety of aryl chlorides.[a]



Entry	ArCl	Amine	Product	Yield [%][b]
1		H_2NBu		81
2		$NHBu_2$		89
3				93
4				91
5				96
6[c]				93
7				94
8				91
9		H_2NBu		92
10				93
11				88
12				92
13		H_2NBu		91
14[d]				87
15[d]				91
16				95

[a] ArCl (1.0 mmol), amine (1.2 mmol), NaO*t*Bu (1.4 mmol), $Pd(OAc)_2$ (0.5 mol%), *t*Bu-Bphos **5** (1.0 mol%), and toluene (2 mL) were heated to 110–115 °C with continuous stirring for 20 h under nitrogen atmosphere. [b] Yield of isolated product. [c] 1 mol% $Pd(dba)_2$ was used (ligand/Pd = 2; dba = dibenzylidene). [d] Cy-Bphos **4** was used.

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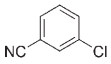
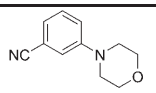
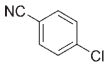
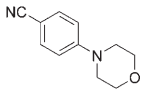
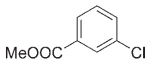
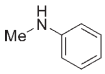
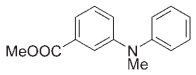
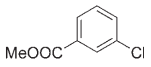
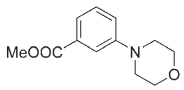
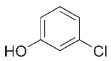
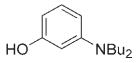
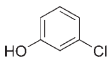
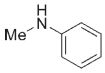
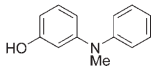
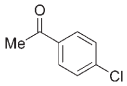
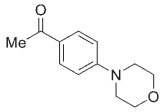
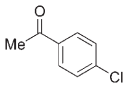
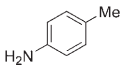
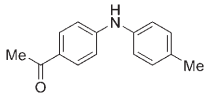
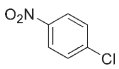
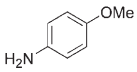
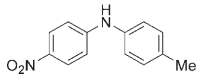
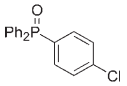
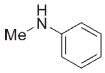
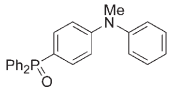
Table 4. Palladium–Bphos-catalyzed amination of functionalized aryl chlorides.[a]

Entry	ArCl	Amine	Product	Yield [%][b]
1				92
2				94
3				91
4[f]				88
5[c,d]		$HNBu_2$		64
6[c,d]				69
7				80
8				44
9[e]				31
10[e]				89

[a] ArCl (1.0 mmol), amine (1.2 mmol), Cs_2CO_3 (1.4 mmol), $Pd(OAc)_2$ (0.5 mol%), *t*Bu-Bphos **5** (1.0 mol%), and toluene (2 mL) were heated to 110–115 °C with continuous stirring for 24 h under nitrogen atmosphere. [b] Yield of isolated product. [c] 1 mol% $Pd(OAc)_2$ was used (ligand/Pd = 2). [d] K_3PO_4 (2.0 mmol) was used. [e] 2 mol% $Pd(OAc)_2$ was used. [f] Cy-Bphos **4** was used.

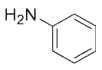
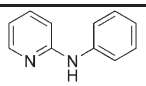
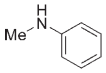
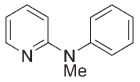
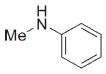
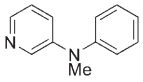
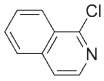
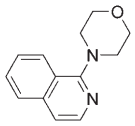
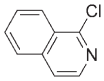
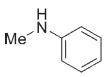
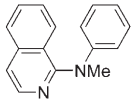
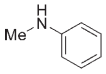
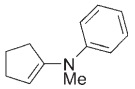
eroaryl chlorides with different amines were performed. The Pd–Bphos complexes were highly effective for both electron-rich and electron-deficient aryl halides. Furthermore, the palladium complex of *t*Bu-Bphos **5** provided high selectivity for monoarylation of aliphatic primary amines (Table 3, entry 1). Cyclic and sterically hindered acyclic secondary amines are good coupling partners in these reactions. Sterically hindered 2-chloro-*m*-xylene was efficiently coupled to a secondary aromatic amine in excellent yield in the presence of Cy-Bphos **4** (Table 3, entry 15). This sterically demanding substrate required the less sterically bulky ligand **4** in the amination reaction. Besides aryl chlorides, aryl bromide substrates were effective even when the experiments were conducted at room temperature (not shown; bromobenzene was coupled with aniline to give diphenylamine in 94% yield at room temperature for 20 h with 0.5 mol% $Pd(OAc)_2$ and 1 mol% **5**).

The amination of functionalized aryl chlorides shows the usefulness of this catalytic system (Table 4). Substrates bearing a base-sensitive functional group were coupled with either primary or secondary amines effectively in the presence of Cs_2CO_3 base.[28] Cyano-, methoxy-, ester-, and diphenylphosphanyl-substituted aryl chlorides also gave high yields (88–94%) of the corresponding anilines. Although we observed that the phenol, methyl ketone, and nitro group were slightly incompatible under these reaction conditions, we obtained the desired products in moderate yields (31–69%). The side reactions were mainly O-arylation of phenol and ketone and α arylation of methyl ketone, as observed by GC–MS analysis.

As heterocycles represent a very important class of compounds in biology and pharmacy,[29] the selective functionalization of these molecules is of great interest. The Pd–Bphos complexes were found to be effective in the amination of *N*-heteroaryl chlorides, which were generally coupled with amines in poor yield due to the coordination of the heteroatom with the active palladium center.[30,31] Heterocycles like 2- or 3-chloropyridine and chloroisoquinoline can also be aminated successfully (87–98%) (Table 5). As a rare example, an alkenyl chloride was found to be a suitable substrate for amination in the presence of a secondary amine (Table 5, entry 6). Notably, when a primary amine was chosen to couple with 1-chloropentene, a significant amount of the corresponding imine side product was obtained.

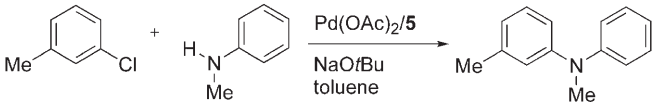
As excellent results were achieved, we further probed the catalyst effectiveness by examining the amination of aryl chlorides under milder reaction conditions and even at lower catalyst concentrations. Nonactivated 3-chlorotoluene was chosen to be the prototypical aryl chloride for coupling with *N*-methylaniline in the presence of $Pd(OAc)_2$ and *t*Bu-Bphos **5**. Under standard reaction conditions (0.5 mol% Pd, 1 mol% ligand, 110 °C), a yield of 97% was obtained (Table 6, entry 1). We were delighted to find that by decreasing the temperature to 50 °C, only a slight decrease in catalytic activity was observed (Table 6, entry 2). The conversion decreased significantly by lowering the catalyst concentration to 0.01 mol% Pd (33% yield determined by GC, turnover number (TON) = 3300; Table 4, entries 3–5). However, when the ligand concentration was increased to 0.1 mol% (ligand/Pd = 10:1) at 140 °C, a good coupling yield of 84% (TON = 8400) was obtained.

Table 5. Palladium–Bphos-catalyzed amination of heteroaryl and alkenyl chlorides.[a]

Entry	Het-ArCl	Amine	Product	Yield [%][b]
1				98
2				97
3				87
4				98
5				93
6				81

[a] ArCl (1.0 mmol), amine (1.2 mmol), NaO*t*Bu (1.4 mmol), $Pd(OAc)_2$ (0.5 mol%), *t*Bu-Bphos **5** (1.0 mol%), and toluene (2 mL) were heated to 110–115 °C with continuous stirring for 24 h under nitrogen atmosphere. [b] Yield of isolated product.

Table 6. Investigation of ligand efficiency in Pd-catalyzed amination of a nonactivated aryl chloride.[a]



Entry	Pd [mol%]	L/Pd	*T* [°C]	Yield [%][b]	TON
1	0.5	2	110	97	194
2	0.5	2	50	92	184
3	0.1	2	110	86	860
4	0.05	2	110	83	1660
5	0.01	2	110	33	3300
6	0.01	10	140	84	8400

[a] 3-Chlorotoluene (1.0 mmol), *N*-methylaniline (1.2 mmol), NaO*t*Bu (1.4 mmol), toluene (2.0 mL, 0.5 M), 24 h. [b] Yields determined by GC authentic sample/dodecane calibration curve.

Conclusions

In summary, we have reported a class of simple and highly active benzamide-derived P,O-type ligands for palladium-catalyzed amination of aryl chlorides. A range of aryl, heteroaryl, and alkenyl chlorides were found to be compatible under these reaction conditions. The high stability of the hemilabile ligand gave relatively high turnover numbers in amination (TON up to 8400). The inexpensiveness of the benzamide starting material as well as the simplicity of the ligand synthesis make this type of hemilabile ligand highly attractive. The variety of readily available ligand precursors (substituted benzoic acid) reflects nicely the modular synthesis. This characteristic is of much importance for obtaining a diverse ligand family, as the synthesis of more-complex molecules by palladium-catalyzed coupling reactions often requires fine-tuning of the catalyst system, especially the ligand scaffold. In general, other known ligands require more-complex chemistry to achieve diversity. In view of the easy modification of the Bphos structure, including the potential enantioselective variants, we anticipate that further enhancements in reactivity as well as versatility of the ligands will be attained.

Experimental Section

General Considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All amination reactions were performed in Rotaflo® (England) HP-6 resealable screw-cap Schlenk flasks (≈20 mL) with oil-bath heating and magnetic stirring. Toluene and THF were distilled from sodium and sodium benzophenone ketyl, respectively, under nitrogen.[32] Chlorodiphenylphosphine and chlorodialkylphosphines were further purified by vacuum distillation prior to use. TMEDA was freshly distilled over Na or CaH_2 under nitrogen. Commercially available aryl chlorides (liquid form only) were purified by passing through a short plug (0.5 cm width × 4 cm height) of neutral alumina or distillation under reduced pressure. Anilines and alkylamines were purified by distillation in the presence of molecular sieves and stored under nitrogen. *N*,*N*-Diethylbenzamide was distilled under reduced pressure and stored under nitrogen atmosphere with 4-Å molecular sieves. A new bottle of *sec*-butyllithium was used (Note: as the concentration of *sec*-BuLi from a previously opened bottle may vary, we recommend that a titration be performed before use). Thin-layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 70–230 and 230–400 mesh) was used for column chromatography. Melting points were measured on an uncorrected Büchi B-545 melting-point instrument. ^{1}H NMR spectra were recorded on a Varian (500 MHz) spectrometer. Spectra were referenced to the residual proton resonance in $CDCl_3$ ($\delta = 7.26$ ppm) or tetramethylsilane (TMS, $\delta = 0.00$ ppm) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS. ^{13}C NMR spectra were recorded on a Varian 500 spectrometer and referenced to $CDCl_3$ ($\delta = 77.0$ ppm). ^{31}P NMR spectra were recorded on a Varian spectrometer and referenced to 85% H_3PO_4 externally. Coupling constants (J) are reported in Hertz (Hz). Mass spectra (EI and FAB) were recorded on an HP 5989B mass spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker APEX 47e FT-ICR mass spectrometer (ESI). GC–MS was conducted on an HP G1800C GCD system with an HP5 MS column (30 m × 0.25 mm). Known products were characterized by NMR spectroscopy and mass spectrometry. Unknown compounds were fully characterized by NMR and IR spectroscopy, MS, and HRMS. The products described with yields determined by GC were accorded the authentic samples/dodecane calibration standard.

Syntheses

General procedure for the preparation of Bphos ligands: Titrated *sec*-BuLi (1.2 mL, 1.1 mmol, 0.92 M in cyclohexane) was added dropwise to freshly distilled TMEDA (0.18 mL, 1.2 mmol) in anhydrous THF (10 mL) at −78 °C (dry ice/acetone bath) under nitrogen. The reaction mixture was stirred for 15 min. A solution of *N*,*N*-diethylbenzamide (177 mg, 1.0 mmol) in THF (7.0 mL) was then added dropwise by cannula (≈5 min), and the mixture was stirred for another 15 min at −78 °C. The level of lithiation was checked by continuous monitoring of a sample aliquot quenched by D_2O. After the addition of chlorodiphenylphosphine (0.35 mL, 1.5 mmol) in THF (5.0 mL) to the reaction mixture at −78 °C, the dry ice/acetone bath was removed, and the mixture was allowed to reach room temperature (≈30 min) with continuous stirring. The mixture

was stirred for another 30 min at 28 °C (room temperature), after which the reaction was quenched with saturated ammonium chloride solution (≈50 mL). The aqueous layer was extracted with diethyl ether (2× ≈50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered over a short silica pad. The solvent was removed by rotary evaporation, and the crude mixture was purified by flash column chromatography on silica gel with hexane/ethyl acetate (9:1) as eluent to afford a colorless oil. A white crystalline solid was obtained upon standing in the freezer overnight.

3: White solid, 224 mg, 62%; m.p.: 149–150 °C; IR: $\tilde{\nu}$= 2923, 2853, 1647, 1460, 1376, 1285, 1174, 1097, 1056, 745, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.31–7.38 (m, 13H), 7.12 (d, J=7.5 Hz, 1H), 3.52–3.53 (m, 2H), 2.94–2.96 (m, 2H), 1.19 (t, J=5.5 Hz, 3H), 0.99 ppm (t, J=5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.0, 143.8, 136.6, 136.5, 134.3, 133.7, 133.6, 128.9, 128.5, 128.3, 128.2, 125.8, 125.7, 42.6, 38.5, 13.8, 12.5 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ=–13.9; MS (EI): m/z (%)= 361 (20) $[M]^+$, 332 (90), 304 (100), 226 (60), 207 (30), 183 (40); HRMS: m/z calcd for $C_{23}H_{24}NOP$: 361.15955; found: 361.15963.

4: White solid, 203 mg, 54%; m.p.: 122–123 °C; IR: $\tilde{\nu}$=2920, 2852, 2724, 1636, 1460, 1376, 1316, 1098, 777, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.51 (d, J=8.0 Hz, 1H), 7.30–7.33 (m, 2H), 7.21 (d, J=7.5 Hz, 1H), 3.67–3.69 (m, 1H), 3.43–3.44 (m, 1H), 3.07–3.09 (m, 2H), 2.09–2.11 (m, 1H), 1.01–1.84 ppm (m, 27H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.6, 132.7, 128.7, 127.4, 125.9, 42.8, 38.7, 35.4 (overlapped), 32.5 (overlapped), 30.1 (overlapped), 28.7, 27.4, 26.8 (overlapped), 26.2 (overlapped), 13.9, 12.6 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ=–8.7 ppm; MS (EI): m/z (%)=373 (100) $[M]^+$; HRMS: m/z calcd for $C_{23}H_{36}NOPH$: 374.2602; found: 374.2613.

5: White solid, 180 mg, 56%; m.p.: 59–60 °C; IR: $\tilde{\nu}$=2922, 2852, 1646, 1460, 1376, 1285, 1174, 1097, 1056, 745, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.78 (d, J=7.0 Hz, 1H), 7.28–7.35 (m, 2H), 7.18 (d, J= 6.0 Hz, 1H), 3.75–7.81 (m, 1H), 3.28–3.35 (m, 1H), 3.10–3.17 (m, 1H), 2.98–3.04 (m, 1H), 1.25 (t, J=6.5 Hz, 3H), 1.14–1.25 (m, 18 Hz), 1.04 ppm (t, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.6, 146.7, 146.4, 135.1, 134.3, 134.1, 128.9, 126.8, 125.9, 125.9, 42.9, 38.2, 32.9, 32.6, 32.4, 32.2, 31.3, 31.1, 30.4, 30.3, 13.9, 12.4 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ=+22.6 ppm; MS (EI): m/z (%)=321 (100) $[M]^+$; HRMS: m/z calcd for $C_{19}H_{32}NOPH$: 322.2300; found: 322.2285.

General procedure for amination of aryl chlorides: Purified ArCl (1.0 mmol, if solid), NaO*t*Bu (1.4 mmol), $Pd(OAc)_2$ (0.5 mol%), *t*Bu-Bphos **5** (1.0 mol%), and magnetic stirrers (3×10 mm) were charged to an oven-dried Schlenk tube. The tube was evacuated and backfilled with nitrogen (3 cycles). Freshly distilled toluene (2.0 mL), ArCl (1.0 mmol, if liquid), and amine (1.2 mmol) were added under nitrogen. The Schlenk tube was resealed and placed on a preheated oil bath with magnetic stirring. The reaction was monitored by GC and TLC analysis. The reaction was allowed to reach room temperature after completion of reaction. Water (≈5 mL) was then added. The reaction mixture was extracted by ethyl acetate (3×≈10 mL). The combined organic phases was washed with brine and dried over Na_2SO_4. The crude mixture was purified by column chromatography on silica gel with hexane/ethyl acetate as the eluent.

N-*n*-butyl-4-toluidine (Table 3, entry 1):[10d] Pale-yellow liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=6.88 (d, J=8.0 Hz, 2H), 6.44 (d, J=8.5 Hz, 2H), 3.20 (brs, 1H), 2.96 (t, J=7.0 Hz, 2H), 2.14 (s, 3H), 1.44–1.47 (m, 2H), 1.31–1.33 (m, 2H), 0.88 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.5, 129.7, 126.5, 113.0, 44.5, 31.8, 21.6, 20.5, 14.3 ppm; MS (EI): m/z (%)=163 (40) $[M]^+$, 120 (100), 91 (20).

N,*N*-di-*n*-butyl-4-toluidine (Table 3, entry 2):[33] ^1H NMR (500 MHz, $CDCl_3$): δ=7.01 (d, J=8.5 Hz, 2H), 6.58 (d, J=8.5 Hz, 2H), 3.23 (t, J= 7.5 Hz, 4H), 2.23 (s, 3H), 1.53–1.55 (m, 4H), 1.33 (m, 4H), 0.95 ppm (t, J=7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.3, 129.6, 124.5, 112.5, 51.1, 29.5, 20.5, 20.1, 13.8 ppm.

N-methyl-*N*-phenyl-4-toluidine (Table 3, entry 3):[25] Yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.60–7.61 (m, 2H), 7.18–7.20 (m, 3H), 6.89 (d, J= 8.0 Hz, 2H), 6.49 (d, J=8.5 Hz, 2H), 3.50 (s, 3H), 2.70 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=152.8, 149.3, 142.7, 129.5, 126.7, 118.9, 116.3, 115.3, 40.8, 22.1 ppm; MS (EI): m/z (%)=197 (100) $[M]^+$, 167 (10).

4-(4-Tolyl)-morpholine (Table 3, entry 4):[34] White solid; ^1H NMR (500 MHz, $CDCl_3$): δ=7.08 (d, J=9.0 Hz, 2H), 6.82 (d, J=9.0, 2H), 3.83–3.86 (m, 4H), 2.27 ppm (s, 3H); MS (EI): m/z (%)=177 (100) $[M]^+$.

N-methyl-*N*-phenyl-3-toluidine (Table 3, entry 5):[10d] Yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.53–7.66 (m, 4H), 7.16–7.39 (m, 5H), 3.65 (s, 3H), 2.68 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.7, 149.6, 139.5, 129.3, 128.7, 125.9, 122.1, 121.5, 118.0, 40.9, 22.3 ppm; MS (EI): m/z (%)=197 (100) $[M]^+$, 167 (20).

4-(4-Methoxyphenyl)morpholine (Table 3, entry 6):[35] White solid; ^1H NMR (500 MHz, $CDCl_3$): δ=6.90 (d, J=9.0 Hz, 2H), 6.85 (d, J= 9.0 Hz, 2H), 3.86 (t, J=5.0 Hz, 4H), 3.77 (s, 3H), 3.06 ppm (t, J=5.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=154.1, 145.6, 117.9, 114.7, 67.1, 55.7, 50.8 ppm.

N-methyl-*N*-(4-methoxyphenyl)aniline (Table 3, entry 7):[36] Light-yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.27–7.28 (m, 2H), 7.13 (d, J= 9.0 Hz, 2H), 6.93 (d, J=9.0 Hz, 2H), 6.80–6.82 (m, 3H), 3.85 (s 3H), 3.31 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=157.1, 149.9, 142.5, 129.3, 126.2, 118.4, 115.9, 114.8, 55.6, 40.9 ppm.

N-(4-methoxyphenyl)pyrrolidine (Table 3, entry 8):[37] Pale-yellow liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=6.85 (d, J=9.0 Hz, 2H), 6.54 (d, J= 8.0 Hz, 2H), 3.76 (s, 3H), 3.21–3.24 (m, 4H), 1.97–200 ppm (m, 4H).

N-butyl-2-methylaniline (Table 3, entry 9):[38] Pale-yellow liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=7.13–7.17 (m, 1H), 7.06 (d, J=7.5 Hz, 2H), 6.62–6.70 (m, 2H), 3.18 (t, J=7.0 Hz, 2H), 2.14 (s, 3H), 1.63–1.70 (m, 2h), 1.44–1.56 (m, 2H), 1.06 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.7, 130.2, 127.6, 121.3, 116.9, 109.3, 43.3, 32.0, 20.6, 17.8, 14.3 ppm; MS (EI): m/z (%)=163 (100) $[M]^+$.

N-methyl-*N*-phenyl-2-toluidine (Table 3, entry 10):[10d] Light-yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.72–7.54 (m, 6H), 7.12–7.13 (m, 1H), 6.98–6.99 (m, 2H), 3.64 (s, 3H), 2.58 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.7, 147.2, 137.3, 131.7, 129.3, 128.7, 127.6, 126.9, 117.2, 113.3, 39.6, 18.4 ppm; MS (EI): m/z (%)=197 (100) $[M]^+$, 182 (50), 167 (20).

N-(2,5-dimethylphenyl)-*N*-methylaniline (Table 3, entry 11):[10d] Yellow liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=7.05–7.06 (m, 3H), 6.89-6.91 (m, 2H), 6.59–6.60 (m, 1H), 6.43–6.45 (m, 2H), 3.11 (s, 3H), 2.19 (s, 3H), 1.99 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.7, 147.0, 137.3, 133.9, 131.6, 129.6, 129.3, 127.7, 117.2, 113.2, 39.6, 21.4, 17.9 ppm; MS (EI): m/z (%)=211 (100) $[M]^+$, 196 (60), 181 (40).

N-(2-methoxyphenyl)benzylamine (Table 3, entry 12):[10a] Light-yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.20–7.41 (m, 5H), 6.77–6.86 (m, 1H), 6.78 (dd, J=8.0, 1.0 Hz, 1H), 6.63–6.70 (m, 1H), 6.57 (dd, J=8.0, 1.0 Hz, 1H), 4.61 (brs, 1H), 4.34 (s, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.8, 139.6, 138.2, 128.6, 127.5, 127.0, 121.3, 116.7, 110.1, 109.4, 55.6, 48.3 ppm.

N-*n*-butyl-2,6-dimethylaniline (Table 3, entry 13):[10d] Light-yellow liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=6.86 (d, J=7.5 Hz, 2H), 6.44 (d, J= 7.5 Hz, 1H), 3.38 (brs, 1H), 2.88 (t, J=7.0 Hz, 2H), 2.18 (s, 6H), 1.46–1.48 (m, 2H), 1.32–1.33 (m, 2H), 0.90 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.9, 129.6, 129.3, 122.1, 49.0, 33.9, 21.1, 19.0, 14.5 ppm; MS (EI): m/z (%)=177 (50) $[M]^+$, 134 (100).

N-benzyl-2,6-dimethylaniline (Table 3, entry 14):[23] Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ =7.26–7.41 (m, 5H), 7.00 (d, J=7.5 Hz, 2H), 6.86 (t, J=8.0 Hz, 1H), 4.11 (s, 2H), 3.20 (brs, 1H), 2.06 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.0, 140.4, 129.9, 128.8, 128.5, 127.9, 127.2, 122.1, 52.8, 18.6 ppm.

N-(2,6-dimethylphenyl)-*N*-methylaniline (Table 3, entry 15):[36] Light-yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.19–7.20 (m, 5H), 6.82 (t, J=7.5 Hz, 1H), 6.59 (d, J=7.5 Hz, 2H), 3.21 (s, 3H), 2.33 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=146.2, 138.8, 136.0, 129.4, 128.7, 125.9, 118.3, 137.6, 41.2, 19.0 ppm.

N-(2,6-dimethylphenyl)aniline (Table 3, entry 16):[36] Light-yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ=7.19–7.20 (m, 5H), 6.82 (t, J=7.5 Hz, 1H), 6.59 (d, J=7.5 Hz, 2H), 5.24 (brs, 1H), 2.33 ppm (s, 6H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ = 146.5, 138.8, 136.0, 129.4, 128.7, 125.9, 118.3, 137.6, 18.9 ppm.

N-(3-cyanophenyl)morpholine (Table 4, entry 1):[39] Light-yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (dd, J = 7.5, 9.0 Hz, 1H), 7.13 (dt, J = 7.5, 1.0 Hz, 1H), 7.08–7.11 (m, 2H), 3.88 (brt, 4H), 3.18 ppm (brt, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.1, 129.8, 122.6, 119.4, 119.2, 117.8, 112.8, 66.3, 48.6 ppm; MS (EI): *m/z* (%) = 188 (50) $[M]^+$, 145 (100).

N-(4-cyanophenyl)morpholine (Table 4, entry 2):[10d] Light-yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 4.07–4.10 (m, 4H), 3.50–3.53 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.9, 132.8, 129.0, 120.2, 114.3, 66.9, 47.4 ppm; MS (EI): *m/z* (%) = 188 (100) $[M]^+$, 130 (100).

N-(3-carbomethoxyphenyl)-*N*-methylaniline (Table 4, entry 3):[25] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (dd, J = 3.0, 1.0 Hz, 1H), 7.55–7.56 (m, 1H), 7.25–7.35 (m, 3H), 7.11 (m, 1H), 7.03–7.10 (m, 3H), 3.80 (s, 3H), 3.34 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 149.6, 147.9, 131.3, 129.5, 129.0, 123.3, 122.4, 121.9, 121.5, 119.0, 52.2, 40.1 ppm.

N-(4-carbomethoxyphenyl)morpholine (Table 4, entry 4):[40] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.5 Hz, 2H), 6.88 (d, 8.5 Hz, 2H), 3.88 (s, 3H), 3.86 (t, J = 5.0 Hz, 4H), 3.29 ppm (t, J = 5.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 154.2, 131.3, 120.6, 113.3, 66.8, 51.3, 47.9 ppm.

N,N-dibutyl-3-aminophenol (Table 4, entry 5):[28] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03–7.06 (m, 1H), 6.23–6.25 (m, 1H), 4.33 (brs, 1H), 3.22 (t, J = 6.0 Hz, 4H), 1.53–5.60 (m, 4H), 1.29–1.98 (m, 4H), 0.98 ppm (t, J = 6.0 Hz, 6H).

N-methyl-*N*-phenyl-3-aminophenol (Table 4, entry 6):[41] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.36 (m, 2H) 7.04–7.11 (m, 4H), 6.41–6.50 (m, 2H), 4.99 (brs, 1H), 3.31 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 150.3, 149.3, 130.7, 129.8, 122.7, 121.9, 111.6, 107.9, 106.3, 41.0 ppm.

N-(4-acetylphenyl)morpholine (Table 4, entry 7):[40] Light-yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.83 (t, J = 5.0 Hz, 4H), 3.30 (t, J = 5.0 Hz, 4H), 2.54 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.9, 154.0, 130.2, 128.3, 113.4, 66.5, 47.6, 26.1 ppm.

N-(4-acetylphenyl)-4-toluidine (Table 4, entry 8):[42] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, J = 9.0 Hz, 2H), 6.87–6.89 (m, 4H), 6.44 (d, J = 8.5 Hz, 2H), 3.23 ppm (brs, 1H).

[4-(*N*-methyl-*N*-phenyl)aminophenyl]diphenylphosphine oxide (Table 4, entry 10):[43] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06–7.66 (m, 17H), 6.84 (dd, J = 9.0, 2.0 Hz, 2H), 3.30 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.0, 147.1, 133.5 (d, $J_{C,P}$ = 103.0 Hz), 133.2 (d, $J_{C,P}$ = 11.0 Hz), 132.4 (d, $J_{C,P}$ = 108.5 Hz), 132.1 (d, $J_{C,P}$ = 9.0 Hz), 131.9, 130.1, 128.6 (d, $J_{C,P}$ = 12.0 Hz), 126.2, 125.7, 114.7 (d, $J_{C,P}$ = 14.0 Hz), 40.9 ppm; ^{31}P NMR (162 MHz): δ = 30.8 ppm; MS (EI): *m/z* (%) = 383 (100) $[M]^+$, 306 (20).

N-(2-pyridyl)aniline (Table 5, entry 1):[44] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, J = 9.0 Hz, 1H), 7.44 (t, J = 8.5 Hz, 1H), 7.00–7.01 (m, 2H), 6.62–6.70 (m, 3H), 6.46 (d, J = 8.5 Hz, 2H), 3.67 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 148.2, 143.3, 138.3, 129.7, 118.9, 116.3, 113.2, 109.6 ppm.

N-(2-pyridyl)-*N*-methylaniline (Table 5, entry 2):[44] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 8.5 Hz, 1H), 7.00–7.01 (m, 2H), 6.62–6.70 (m, 3H), 6.46 (d, J = 8.5 Hz, 2H), 2.68 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3, 149.2, 148.0, 138.3, 129.7, 118.9, 116.3, 113.5, 109.2, 41.3 ppm.

N-(3-pyridyl)-*N*-methylaniline (Table 5, entry 3):[10d] Light-yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, J = 2.5 Hz, 1H), 8.01–8.03 (m, 1H), 7.17–7.19 (m, 2H), 7.11 (m, 1H), 6.96–7.00 (m, 4H), 3.02 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.8, 145.3, 141.7, 130.0, 128.6, 124.9, 123.8, 123.7, 122.8, 40.6 ppm.

N-(1-isoquinolinyl)morpholine (Table 5, entry 4): Purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1). White solid; R_f = 0.2 (hexane/ethyl acetate = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 5.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 5.5 Hz, 1H), 3.96 (t, J = 4.5 Hz, 4H), 3.39 ppm (t, J = 4.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1, 140.6, 138.0, 129.6, 127.1, 126.1, 125.2, 121.5, 116.1, 67.0, 51.8 ppm; MS (EI): *m/z* (%) = 214 (100) $[M]^+$; HRMS: *m/z* calcd for $C_{13}H_{14}N_2OH$: 215.1184; found: 215.1185.

N-(1-isoquinolinyl)-*N*-methylaniline (Table 5, entry 5): Purified by column chromatography on silica gel (hexane/ethyl acetate = 30:1). Yellow solid; R_f = 0.5 (hexane/ethyl acetate = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 5.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 5.5 Hz, 1H), 7.03–7.04 (m, 2H), 6.58–6.59 (m, 1H), 6.43 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 150.7, 141.1, 138.2, 129.5, 129.2, 126.9, 126.7, 122.8, 122.1, 121.1, 116.7, 41.3 ppm; MS (EI): *m/z* (%) = 234 (100) $[M]^+$; HRMS: *m/z* calcd for $C_{16}H_{14}N_2H$: 235.1235; found: 235.1239.

N-methyl-*N*-(1-cyclopentenyl)aniline (Table 5 entry 6):[45] Light-yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.31 (m, 2H), 7.01–7.07 (m, 3H), 4.73 (s, 1H), 3.15 (s, 3H), 2.32–2.44 (m, 4H), 1.85–1.95 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.4, 149.0, 128.8, 123.3, 122.8, 102.9, 41.4, 32.9, 30.9, 23.4 ppm.

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