New Ligands for a General Palladium-Catalyzed Amination of Aryl and Heteroaryl Chlorides

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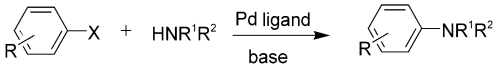
Abstract: The synthesis and application of monodentate *N*-substituted heteroarylphosphines is described. In general, the ligands are conveniently prepared by selective metallation at the 2-position of the respective *N*-substituted heterocycle (pyrrole, indole) by using *n*-butyllithium/tetramethylethylenediamine (TMEDA) followed by quenching with dialkyl- or diarylchlorophosphines. Of the different ligands prepared, the new dialkyl-2-(*N*-arylindolyl)phosphines (cata*CX*ium® P) perform excellently in the palladium-catalyzed amination of aryl and heteroaryl chlorides. Coupling of both activated and deactivated chloroarenes proceeds under mild conditions (room temperature to 60 °C). By using optimized conditions remarkable catalyst productivity (total turnover number, TON, up to 8000) and activity (turnover frequency, TOF = 14000 h^{-1} at 75 % conversion) are observed.

Keywords: amination · anilines · aryl chlorides · catalysis · palladium · phosphines

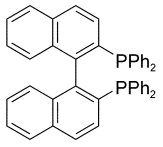
Introduction

Aromatic amines (anilines) are of fundamental interest in the fine chemical industry owing to their importance as building blocks for pharmaceuticals, agrochemicals, and new materials. Since the mid 1990s an elegant approach has been developed for the synthesis of these compounds based on the direct coupling of aryl halides and amines. This so-called "Buchwald–Hartwig amination" reaction occurs in the presence of palladium catalysts with various phosphine ligands and an excess of base (Scheme 1).[1]

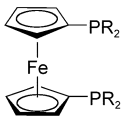
Clearly, this relatively new methodology for C–N bond formation has already become one of the most important tools in the laboratory scale synthesis of aryl amines.[2] Of the different substrates that are available, economically attractive aryl *chlorides* require special catalyst design for successful coupling, unlike aryl iodides or bromides. This is either a consequence of the thermodynamics (experimental bond dissociation energies have been found to be 402, 339, and 272 kJ mol^{-1} at 298 K for chloro-, bromo-, and iodobenzene, respectively)[3] or kinetics, depending on the reaction conditions.[4] With regard to catalyst development, tri-*o*-tolylphosphine[5] was originally used as the ligand, but this phosphine gave poor results with primary amines and did not work with nonactivated aryl chlorides. Next, chelating bis-phosphine ligands like 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[6] and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) or 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D*t*BPF)[7] (**1**–**3**) were introduced as a second generation of catalysts, and have been shown to be efficient with primary amines under mild conditions.



Scheme 1. Pd-catalyzed amination of aryl halides.



1



2 R = Ph
3 R = *t*Bu

Nevertheless, these ligands did not give satisfactory results when aryl chlorides were used as substrates. Later, the use

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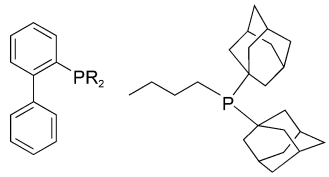
of tri-*tert*-butylphosphine in a general amination protocol of aryl chlorides was reported by Koie and co-workers.[8] Unfortunately, this commercially available ligand is highly sensitive to air, which limits its applications. Wolfe and Buchwald synthesized sterically demanding basic phosphines, such as *o*-(dicyclohexylphosphino)biphenyl (**4**) or *o*-(di-*tert*-butylphosphino)biphenyl ligands (**5**), which are more stable

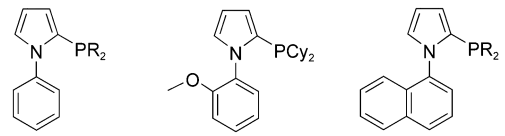


4 R = Cy
5 R = *t*Bu

6

in air and allow room temperature aminations of aryl chlorides.[9] More recently, our group reported di-1-adamantyl(*n*-butyl)phosphine (**6**)[10] to be a very active ligand for the coupling of a wide range of sterically congested aryl chlorides with hindered amines.[11] This now commercially available ligand (cata*CX*ium® A) is more stable than the $P(tBu)_3$ system. In addition, it should be noted that *N*-heterocyclic carbenes have also been used successfully for the amination of aryl chlorides.[12] However the use of carbene ligands generally results in lower catalyst productivity than is the case with phosphine ligands.[13]

We have a long-standing interest in the practical application of palladium-catalyzed coupling reactions.[14] In this respect the stability, productivity, modular variation and ease of preparation of the known catalysts for Buchwald–Hartwig aminations of chloroarenes can still be improved. Very recently, we reported the synthesis of a new class of monophosphine ligands based on the 2-phosphino-*N*-arylpyrrole structure (**7**–**13**) by selective *ortho*-metallation of the corresponding pyrrole and subsequent reaction with R_2PCl.[15]

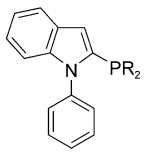


7 R = Ph
8 R = Cy
9 R = *t*Bu
10 R = 1-Ad

11

12 R = Cy
13 R = *t*Bu

Most of these ligands led to extremely efficient catalysts for the Suzuki cross-coupling of aryl chlorides.[15] Here, we describe for the first time a full account of our synthesis of 2-phosphino-*N*-arylpyrroles. Furthermore, the synthesis of new 2-phosphino-*N*-arylindole ligands (**14**–**16**) is presented as well as the application of the pyrrole- and indole-based ligands to the palladium-catalyzed amination of aryl and heteroaryl chlorides



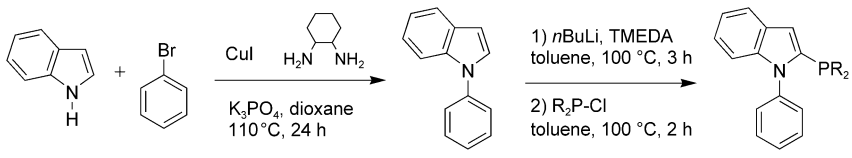
14 R = Cy
15 R = *t*Bu
16 R = 1-Ad

Results and Discussion

Based on the work of Faigl and co-workers, who have shown that *N*-arylpyrroles can be deprotonated selectively at the α-position to the nitrogen atom,[16] we have synthesized different 2-phosphino-*N*-arylpyrroles (**7**–**13**). Typically the corresponding *N*-arylpyrrole was deprotonated by using a mixture of *n*BuLi (1.0 equiv) and TMEDA (1.5 equiv) in hexane. For selective deprotonation *ortho* to the nitrogen atom the use of an excess of TMEDA proved to be crucial. After refluxing the reaction mixture, the intermediate carbanion was trapped with a solution of the respective chlorophosphine. In all cases the phosphines were obtained after crystallization with purities >95%. Clearly this efficient protocol should be applicable to other *N*-arylpyrroles that are commercially available or that are easily synthesized from anilines[17] or by palladium-[18] or copper-catalyzed[19] arylation of pyrrole. In addition, we thought that other heterocycles, for example, indoles, could also be used as substrates. Thus, we prepared *N*-phenylindole by copper-catalyzed arylation of indole with bromobenzene in 85% yield.[19a] Subsequent deprotonation with *n*BuLi/TMEDA and reaction with chlorodicyclohexylphosphine, chlorodi-1-adamantylphosphine and chlorodi-*tert*-butylphosphine gave the ligands **14**–**16**, without much optimization, in yields of 45 to 60% (Scheme 2).

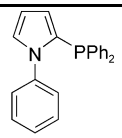
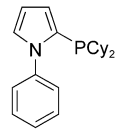
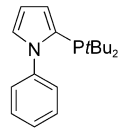
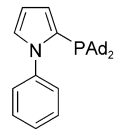
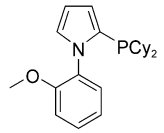
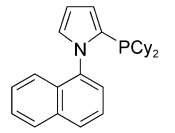
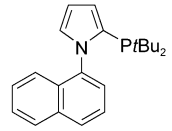
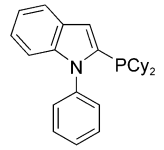
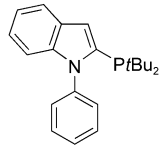
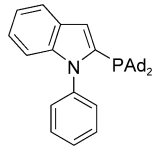
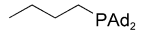
Initially, ligands **7**–**16** were tested in the coupling of chlorobenzene with aniline, which is one of the more difficult aminations to perform, by using previously optimized reaction conditions (Table 1).[11]

As shown in Table 1, when simple phenyl- or cyclohexyl-substituted pyrrole or indole derivatives were used, poor results were obtained (ligands **7**, **8**, and **14**; Table 1, entries 1, 2, and 8). Apparently the steric demand of the ligands is not sufficient to allow the formation of active catalysts. However, when the *N*-phenyl ring was substituted the catalytic activity increased to give yields of up to 68% (ligands **11** and



Scheme 2. Synthesis of *N*-phenylindole-based phosphine ligands.

Table 1. Amination[a] of chlorobenzene with aniline using ligands **7**–**16**.

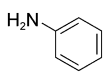
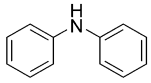
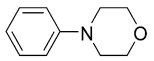
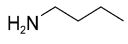
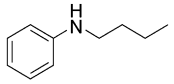
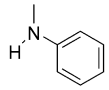
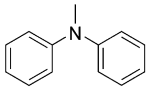
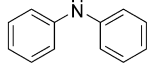
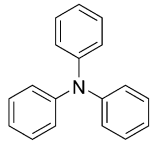
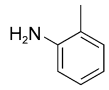
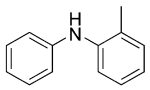
Entry	Ligand	Conv. [%][b]	Yield [%][b]	TON
1		2	1	2
2		11	9	18
3		100	95	190
4		77	76	152
5		62	62	124
6		69	68	136
7		91	87	174
8		13	9	18
9		100	95	190
10		49	46	92
11		96	85	170
12	$P(tBu)_3$	99	92	184

[a] 5 mmol aryl chloride, 6 mmol amine, 6 mmol NaO*t*Bu, 0.5 mol % $Pd(OAc)_2$, 1 mol % ligand, 5 mL toluene, 48 h, 120 °C. [b] Average of 2 runs, determined by GC using diethylene glycol di-*n*-butyl ether as internal standard.

12; Table 1, entries 5 and 6). When *tert*-butylphosphino derivatives were used, better conversions and yields were obtained (up to 95 % yield) due to the increase in the steric demand of the ligands (ligands **9**, **13**, and **15**; Table 1, entries 3, 7, and 9). We have demonstrated that these new ligands work at least as well as "state-of-the-art" ligands, such as $P(tBu)_3$ and di-1-adamantyl(*n*-butyl)phosphine (cata*CX*ium® A), in the chloroarene amination test reactions (Table 1, entries 11 and 12).

The general usefulness of the new ligands is shown in Tables 2 and 3. The reactions of 15 aryl and heteroaryl chlorides with different amines were performed. In most cases the corresponding anilines were obtained in good to excellent yield (>90 %) at low catalyst concentration (0.5 mol % Pd). Chlorobenzene can be coupled efficiently with aliphatic amines (Table 2, entries 2 and 3). Primary and

Table 2. Palladium-catalyzed aminations[a] of chlorobenzene using ligand **15**.

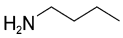
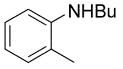
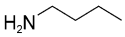
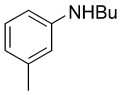
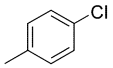
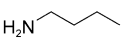
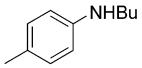
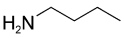
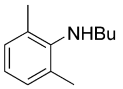
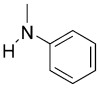
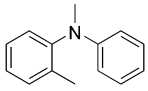
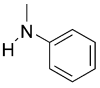
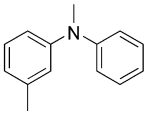
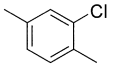
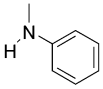
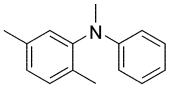
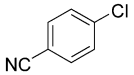
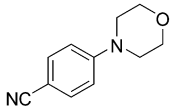
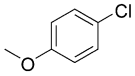
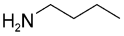
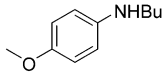
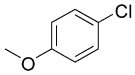
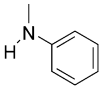
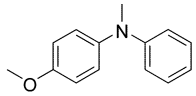
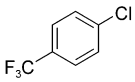
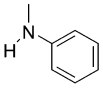
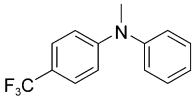
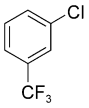
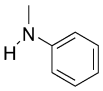
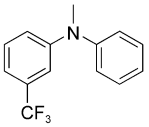
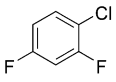
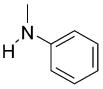
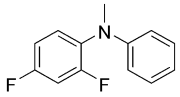
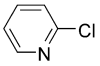
Entry	Amine	Product	Conv. [%][b]	Yield [%][b]
1[c]			100	95
2			100	97
3			100	91
4			100	94
5[d]			100	99
6			100	95

[a] 5 mmol chlorobenzene, 6 mmol amine, 6 mmol NaO*t*Bu, 0.5 mol % $Pd(OAc)_2$, 1 mol % ligand **15**, 5 mL toluene, 20 h, 120 °C. The reaction time has not been minimized. [b] Average of 2 runs, determined by GC using diethylene glycol di-*n*-butyl ether or hexadecane as internal standard. [c] 48 h. [d] Ligand **12** was used.

secondary aromatic amines proved to be efficient coupling partners, too (Table 2, entries 1, 4–6). In the case of the hindered diphenylamine a better result was obtained by using the sterically less demanding ligand **12** instead of **15**.

The amination of functionalized aryl and heteroaryl halides with aliphatic and aromatic amines shows the usefulness of our catalytic system (Table 3). For example, excellent results (88–99 % yield) were obtained with different chlorotoluenes and chloroxylenes (Table 3, entries 1–7). Cyano-, methoxy-, and fluoro-substituted aryl chlorides also gave high yields (75–98 %) of the corresponding anilines (Table 3, entries 8–13). Heterocycles like 2- or 3-chloropyridine can also be aminated successfully (90–99 % yield; Table 3, en-

Table 3. Amination[a] of functionalized aryl and heteroaryl chlorides using ligand **14** or **15**.

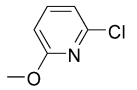
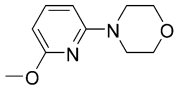
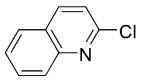
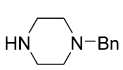
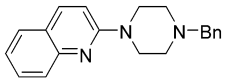
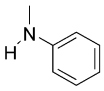
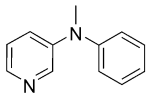
Entry	Aryl chloride	Amine	Product	Conv. [%][b]	Yield [%][b]
1				100	99
2				100	88
3				100	95
4				100	95
5				100	92
6				100	95
7				100	91
8[c]				100	75
9				100	88
10				100	90
11				100	97
12				100	98
13				100	98
14				100	60 (**15**) 99 (**14**)
15[c]				100	92
16				100	77 (**15**) 99 (**14**)

tries 14–19). In some cases the sterically less demanding ligand **14** gave superior results than ligand **15**.

Owing to the excellent results obtained, we investigated the amination of aryl chlorides under milder reaction conditions and at lower catalyst concentrations. As a model system for a nonactivated aryl chloride, 3-chlorotoluene was treated with *N*-methylaniline in the presence of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)-*N*-phenylindole (**15**) as the catalyst system (Table 4).

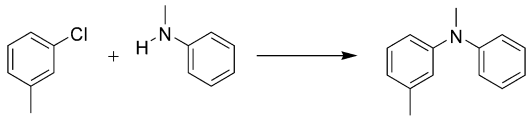
Under standard conditions (0.5 mol% Pd, 1 mol% ligand, 120°C), a yield of 95% was obtained (Table 4, entry 1). We were surprised to find that by decreasing the temperature to

Table 3. (Continued)

Entry	Aryl chloride	Amine	Product	Conv. [%][b]	Yield [%][b]
17				100	99 (**14**)
18				100	90
19[c]				100	99

[a] 5 mmol aryl chloride, 6 mmol amine, 6 mmol NaO*t*Bu, 0.5 mol % $Pd(OAc)_2$, 1 mol % ligand, 5 mL toluene, 20 h, 120 °C. The reaction time has not been minimized. [b] Average of 2 runs, determined by GC using diethylene glycol di-*n*-butyl ether or hexadecane as internal standard. [c] 1 mol % $Pd(OAc)_2$, 2 mol % ligand.

Table 4. Reaction conditions for the reaction of 3-chlorotoluene with *N*-methylaniline.[a]



Entry	Pd [mol %]	L/Pd	*T* [°C]	Conv. [%][b]	Yield [%][b]	TON
1	0.5	2	120	100	95	190
2	0.5	2	80	100	90	180
3	0.5	2	40	100	90	180
4	0.25	2	120	100	91	364
5	0.1	2	120	98	86	860
6	0.05	2	120	83	73	1460
7	0.025	2	120	70	62	2480
8	0.025	10	120	78	67	2680
9	0.025	10	140	92	80	3200
10	0.01	2	120	24	23	2300
11	0.01	50	120	45	37	3700
12	0.01	50	140	100	80	8000

[a] 5 mmol 3-chlorotoluene, 6 mmol *N*-methylaniline, 6 mmol NaO*t*Bu, $Pd(OAc)_2$, ligand **15**, 5 mL toluene, 20 h. The reaction time has not been minimized. [b] Average of 2 runs, determined by GC using diethylene glycol di-*n*-butyl ether as internal standard.

40 °C, only a slight decrease in the activity was observed (Table 4, entries 2 and 3). At a higher temperature the conversion decreased in parallel with the decrease in catalyst loading. The conversion decreased significantly by lowering the catalyst concentration to 0.01 mol % Pd (23 % yield; turnover number (TON) 2300; Table 4, entry 10). However, by increasing the ligand concentration to 0.5 mol % (L/Pd 50:1) and by raising the temperature to 140 °C a good coupling yield of 80 % (TON = 8000) was obtained. In addition to catalyst productivity studies, we also investigated the activity of the catalyst. While most of the reactions were simply performed for a standard reaction time (e.g., 20 h), catalyst activity was measured by using the conditions described in Table 4, entry 12. We found that this catalyst system has a comparably high activity. Even after 30 min approximately 75 % conversion and 70 % product yield were obtained; this corresponds to a turnover frequency (TOF) of 14000 h^{-1}. Naturally, even higher turnover frequencies can be expected at lower conversion.

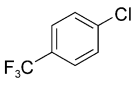
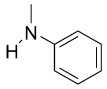
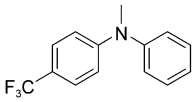
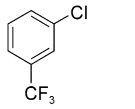
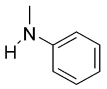
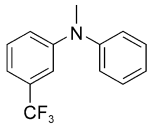
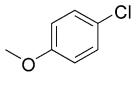
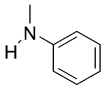
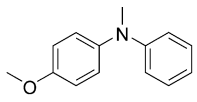
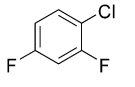
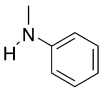
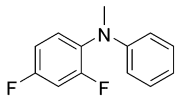
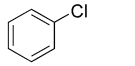
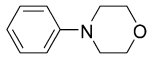
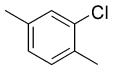
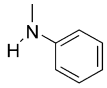
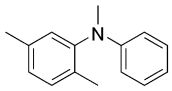
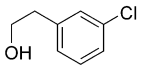
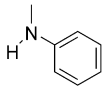
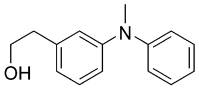
Finally, the amination of different aryl chlorides at low temperatures was studied in more detail. Table 5 demonstrates that excellent results can be obtained at room temperature with activated aryl chlorides by using 1 mol % catalyst (Table 5, entries 1 and 2). For nonactivated and deactivated aryl chlorides, high yields (> 90 %) of the corresponding anilines were obtained at a temperature of 60 °C. Owing to the mild conditions the new catalyst system seems to be useful for more sensitive substrates, too (e.g., Table 5, entry 7).

Conclusions

Monodentate *N*-substituted heteroarylphosphines have been conveniently synthesized by selective metallation at the 2-position of the respective *N*-substituted heterocycle (pyrrole, indole). The variety of available ligands (**7**–**16**) reflects nicely the modular synthesis. This is very important, since the synthesis of more complex molecules by palladium-catalyzed coupling reactions often requires fine-tuning of the catalytic system. In general, other known ligands require more complex chemistry to achieve diversity.

For the first time palladium-catalyzed aminations of aryl halides have been performed in the presence of *N*-substituted heteroarylphosphines. In general, excellent results have been obtained for the coupling of a variety of aryl and heteroaryl chlorides in the presence of dialkylphosphino-*N*-arylindoles **14** and **15**. Remarkably, high yields (> 90 %) were obtained under mild conditions (RT to 60 °C). On the other hand excellent catalyst productivity (TON 8000) and activity (TOF = 14000 h^{-1} at 75 % conversion) were observed for the model reaction of 3-chlorotoluene and *N*-methylaniline at a higher reaction temperature. Owing to their excellent catalytic performance and convenient preparation this class of ligands will be commercially available from 2004 under the trade name cata*CX*ium® P.

Table 5. Amination[a] of aryl chlorides at low temperatures.

Entry	Aryl chloride	Amine	Product	T [°C]	Yield [%][b]
1[c]				25	97
2[c]				25	98
3				60	91
4				60	98
5				60	97
6				60	91
7[d]				65	64

[a] 5 mmol aryl chloride, 6 mmol amine, 6 mmol NaO*t*Bu, 0.5 mol% $Pd(OAc)_2$, 1 mol% ligand **15**, 5 mL toluene, 20 h. The reaction time has not been minimized. [b] Average of 2 runs, determined by GC using diethylene glycol di-*n*-butyl ether or hexadecane as internal standard. [c] 1 mol% $Pd(OAc)_2$, 2 mol% ligand **15**. [d] 1 mmol aryl chloride, 1.2 mmol amine, 1.2 mmol NaO*t*Bu.

Experimental Section

General: Ligands were synthesized and stored under an inert atmosphere using Schlenk techniques. All starting materials and reactants were used as received from commercial suppliers, except TMEDA which was distilled and degassed before use. NMR spectra were recorded on an ARX 400 (Bruker) spectrometer; chemical shifts are given in ppm and are referenced to TMS (^{1}H, ^{13}C NMR), H_3PO_4 (80% in water; ^{31}P NMR) and $CFCl_3$ (^{19}F NMR). IR spectra were recorded on a Magna-IR-series 550 (Nicolet) spectrometer. Mass spectra were recorded on an AMD 402 double focusing, magnetic sector spectrometer (AMD Intectra). GC-MS spectra were recorded on a HP 5989A (Hewlett Packard) chromatograph equipped with a quadrupole analyzer. Gas chromatographic analyses were realized on a HP 6890 (Hewlett Packard) chromatograph using a HP 5 column.

Synthesis of *N*-phenylindole: Dioxane (50 mL), followed by 1,2-diaminocyclohexane (1 mL, 8 mmol) and bromobenzene (6.2 mL, 60 mmol) were added to a mixture of CuI (0.38 g, 2 mmol), indole (4.6 g, 40 mmol), and K_3PO_4 (17.6 g, 42 mmol). The mixture was stirred for 24 h at 110°C, and then diluted with ethyl acetate (30 mL). The blue precipitate was removed by filtration through a plug of silica to give a yellow solution. Concentration under vacuum gave rise to an orange oil that was subjected to column chromatography (silica, ethyl acetate/hexane 10/90) to afford the pure product as a yellow liquid (6.85 g, 35 mmol). Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$–6.88 (m, 10H), 6.45 ppm (d, $^3J(H,H) = 4.7$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 140.0$, 136.1, 130.8, 129.8, 128.2, 124.6, 122.6, 121.4, 120.6, 110.7, 103.8 ppm; MS (EI, 70 eV): m/z (%): 193 (100) [M^+], 165 (18), 89 (9), 77 (6); HRMS: calcd for $C_{14}H_{11}N$: 193.08914; found: 193.08791.

Synthesis of *N*-phenylindole-based phosphine ligands: In a three-necked 100 mL round-bottomed flask equipped with a reflux condenser, *N*-phenylindole (2.9 g, 15 mmol) was dissolved in toluene (30 mL) under argon. TMEDA (3.35 mL, 22.5 mmol) was added followed by *n*BuLi (1.6 M in hexane, 7.2 mL, 15 mmol) at room temperature. The reaction mixture was refluxed for 3 h to obtain a red solution. A solution of the corresponding chlorophosphine (15 mmol in 15 mL of toluene) was slowly added through a syringe. The mixture was refluxed for a further 2 h. After cooling to room temperature, degassed water (15 mL) was added and the mixture was stirred to give a clear solution. The aqueous layer was extracted with toluene (2 × 15 mL), and the combined organic layers were washed with degassed water (15 mL). The solution was dried over $MgSO_4$ and concentrated at 45°C under vacuum to give a yellow viscous liquid which was recrystallized from methanol or hexane.

2-(Dicyclohexylphosphino)-*N*-phenylindole (14): White solid (cryst from hexane); yield 60%; m.p. 157–159°C; ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.69$ (m, 1H), 7.53–7.42 (m, 3H), 7.32 (m, 2H), 7.14 (m, 3H), 6.85 (s, 1H), 1.72–1.65 (m, 11H), 1.27–1.02 ppm (m, 11H); ^{13}C NMR (101 MHz, C_6D_6): $\delta =$ 140.3, 138.9, 137.4, 137.3, 129.9 (d, $^2J(C,P) = 2.9$ Hz), 129.0, 128.2, 128.0, 122.3, 120.3, 111.0, 110.2 (d, $^1J(C,P) =$ 3.8 Hz), 30.3 (d, $^1J(C,P) = 15.3$ Hz), 27.4 (d, $^2J(C,P) = 12.4$ Hz), 27.2 (d, $^3J(C,P) = 8.6$ Hz), 26.6 ppm; ^{31}P NMR (162 MHz, C_6D_6): $\delta = -24.8$ ppm; IR (KBr): $\tilde{\nu} = 3059.3$, 2924.1, 2847.0, 2637.2, 1596.8, 1496.3, 1307.6, 1145.0, 737.2, 695.9 cm^{-1}; MS (70 eV, EI): m/z (%): 389 (48) [M^+], 306 (90), 224 (100), 193 (17), 83 (8), 55 (25), 41 (19); HRMS: calcd for $C_{26}H_{32}NP$: 389.22723; found: 389.22922.

2-(Di-*tert*-butylphosphino)-*N*-phenylindole (15): Pale yellow solid (cryst from MeOH); yield 50%; m.p. 90–92°C; ^{1}H NMR (400 MHz, C_6D_6): $\delta =$ 8.01 (m, 1H), 7.82–7.74 (m, 3H), 7.58 (m, 2H), 7.45 (m, 2H), 7.41 (s, 1H), 7.32 (m, 1H), 1.50 ppm (d, $^3J(H,P) = 12.3$ Hz, 18H); ^{13}C NMR (101 MHz, C_6D_6): $\delta = 140.1$, 139.6, 138.1, 137.9, 130.5 (d, $^2J(C,P) =$ 2.9 Hz), 129.2, 128.4, 128.1, 122.7, 120.8, 120.5, 116.6 (d, $^1J(C,P) = 5.7$ Hz), 33.2 (d, $^1J(C,P) = 18.1$ Hz), 30.6 ppm (d, $^2J(C,P) = 15.3$ Hz); ^{31}P NMR (162 MHz, C_6D_6): $\delta = 5.85$ ppm; IR (KBr): $\tilde{\nu} = 3058.7$, 2937.1, 2892.3, 2857.8, 1595.9, 1496.8, 1469.2, 1361.9, 763.1, 742.4, 700.0 cm^{-1}; MS (EI, 70 eV): m/z (%): 337 (42) [M^+], 281 (30), 224 (100), 193 (19), 57 (30), 41 (20); HRMS: calcd for $C_{22}H_{28}NP$: 337.19595; found: 337.19584.

2-(Di-1-adamantylphosphino)-*N*-phenylindole (16): White solid (cryst from hexane); yield 45%; m.p. 308–310°C; ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.58$ (m, 1H), 7.42–7.33 (m, 3H), 7.15 (m, 2H), 6.98 (m, 3H), 6.82 (m, 1H), 1.89–1.55 ppm (m, 30H); ^{13}C NMR (101 MHz, CD_2Cl_2): $\delta = 141.8$, 141.2, 137.2, 136.5, 132.6 (d, $^2J(C,P) = 2.9$ Hz), 131.2, 130.2, 130.0, 124.5, 122.8, 122.3, 114.3 (d, $^1J(C,P) = 5.7$ Hz), 43.8 (d, $^1J(C,P) = 12.4$ Hz), 39.7, 35.2 (d, $^2J(C,P) = 8.6$ Hz), 33.9 ppm; ^{31}P NMR (162 MHz, CD_2Cl_2): $\delta =$ 6.05 ppm; IR (KBr): $\tilde{\nu} = 3054.7$, 2903.2, 2846.9, 1597.1, 1498.1, 1448.6, 1342.6, 1209.8, 731.1, 649.1 cm^{-1}; MS (EI, 70 eV): m/z (%): 493 (46) [M^+], 358 (16), 135 (100), 93 (16); HRMS: calcd for $C_{34}H_{40}NP$: 493.28983; found: 493.28781.

Catalytic amination of aryl chlorides: A 30 mL pressure tube was loaded with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), the ligand (0.050 mmol), and NaO*t*Bu (577 mg, 6.0 mmol) and was purged by argon. Then, toluene (5 mL), the aryl chloride (5 mmol) and the amine (6 mmol) were added successively under argon. The mixture was stirred for 20 h at 120°C. After cooling to room temperature the mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL). The organic phase was dried over $MgSO_4$, concentrated under vacuum and the product was iso-

lated by column chromatography (silica, ethyl acetate/hexane 10:90). Alternatively, diethylene glycol di-*n*-butyl ether or hexadecane was added as an internal standard and quantitative analysis was performed by using gas chromatography. The commercially available products were identified by comparison of their GC-MS data with the data of authentic samples; known products were characterized by NMR and mass spectroscopy, unknown products were characterized by NMR, IR, MS, and high-resolution MS (HRMS) spectroscopy.

Diphenylamine: MS (EI, 70 eV): *m*/*z* (%): 169 (100) [M^+], 84 (17), 77 (12), 51 (12).

***N*-Phenylmorpholine**: MS (EI, 70 eV): *m*/*z* (%): 163 (85) [M^+], 105 (100), 77 (27).

***N*-*n*-Butylaniline**: MS (EI, 70 eV): *m*/*z* (%): 149 (17) [M^+], 106 (100), 77 (17).

Methyldiphenylamine: MS (EI, 70 eV): *m*/*z* (%): 183 (100) [M^+], 167 (27), 104 (10), 91 (9), 77 (21), 51 (9).

Triphenylamine: MS (EI, 70 eV): *m*/*z* (%): 245 (100) [M^+], 167 (2), 77 (12).

***N*-Phenyl-2-toluidine**: Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 (m, 5H), 6.95 (m, 4H), 5.39 (br s, 1H), 2.28 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1, 141.4, 131.1, 129.5, 128.5, 126.9, 122.2, 120.6, 118.9, 117.6, 18.1 ppm; MS (EI, 70 eV): *m*/*z* (%): 183 (100) [M^+], 106 (20), 91 (18).

***N*-*n*-Butyl-2-toluidine**: Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (m, 1H), 6.91 (m, 1H), 6.50 (m, 2H), 3.25 (br s, 1H), 3.00 (t, ^3J(H,H) = 7.0 Hz, 2H), 1.98 (s, 3H), 1.51 (m, 2H), 1.32 (m, 2H), 0.85 ppm (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3, 128.9, 126.1, 120.5, 115.5, 108.5, 42.6, 30.7, 19.4, 16.4, 12.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 163 (40) [M^+], 120 (100), 91 (20).

***N*-*n*-Butyl-3-toluidine**: Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (m, 1H), 6.42 (m, 1H), 6.31 (m, 2H), 3.34 (br s, 1H), 2.99 (t, ^3J(H,H) = 7.0 Hz, 2H), 2.18 (s, 3H), 1.49 (m, 2H), 1.33 (m, 2H), 0.86 ppm (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.1, 139.4, 129.6, 118.5, 113.9, 110.4, 44.2, 32.2, 22.1, 20.8, 14.4 ppm; MS (EI, 70 eV): *m*/*z* (%): 163 (40) [M^+], 120 (100), 91 (20).

***N*-*n*-Butyl-4-toluidine**: Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, ^3J(H,H) = 7.9 Hz, 2H), 6.43 (d, ^3J(H,H) = 8.5 Hz, 2H), 3.26 (br s, 1H), 2.97 (t, ^3J(H,H) = 7.1 Hz, 2H), 2.14 (s, 3H), 1.48 (m, 2H), 1.32 (m, 2H), 0.85 ppm (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.6, 129.9, 126.5, 113.1, 44.3, 31.9, 20.6, 20.5, 14.2 ppm; MS (EI, 70 eV): *m*/*z* (%): 163 (30) [M^+], 120 (100), 91 (15).

***N*-*n*-Butyl-2,6-dimethylaniline**: Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, ^3J(H,H) = 7.5 Hz, 2H), 6.70 (t, ^3J(H,H) = 7.4 Hz, 1H), 3.36 (br s, 1H), 2.88 (t, ^3J(H,H) = 7.0 Hz, 2H), 2.18 (s, 6H), 1.47 (m, 2H), 1.32 (m, 2H), 0.85 ppm (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.9, 129.6, 129.3, 122.0, 48.5, 33.9, 20.9, 19.0, 14.5 ppm; MS (EI, 70 eV): *m*/*z* (%): 177 (40) [M^+], 134 (100), 105 (20).

***N*-Methyl-*N*-phenyl-2-toluidine**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.56 (m, 6H), 7.14 (m, 1H), 6.97 (m, 2H), 3.65 (s, 3H), 2.58 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.6, 147.3, 137.3, 131.8, 129.4, 128.8, 127.9, 129.9, 117.3, 113.3, 39.5, 18.3 ppm; MS (EI, 70 eV): *m*/*z* (%): 197 (100) [M^+], 182 (43), 167 (21), 77 (20).

***N*-Methyl-*N*-phenyl-3-toluidine**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.53 (m, 4H), 7.41–7.17 (m, 5H), 3.67 (s, 3H), 2.69 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7, 149.6, 139.5, 129.7, 128.8, 125.9, 122.0, 121.5, 120.6, 118.5, 40.8, 22.1 ppm; MS (EI, 70 eV): *m*/*z* (%): 197 (100) [M^+], 167 (10), 77 (12).

***N*-(2,5-Dimethylphenyl)-*N*-methylaniline**: Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (m, 3H), 6.88 (m, 2H), 6.59 (m, 1H), 6.43 (m, 2H), 3.10 (s, 3H), 2.19 (s, 3H), 1.99 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7, 147.1, 137.7, 133.9, 131.6, 129.5, 129.3, 127.7, 117.2, 113.3, 39.5, 21.4, 17.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 211 (100) [M^+], 196 (56), 181 (41), 134 (7), 91 (11), 77 (15).

***N*-(4-Cyanophenyl)morpholine**: Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 9.1 Hz, 2H), 7.11 (d, ^3J(H,H) = 9.1 Hz, 2H), 4.09 (m, 4H), 3.52 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.9, 133.9, 129.3, 120.3, 144.5, 66.9, 47.7 ppm; MS (EI, 70 eV): *m*/*z* (%): 188 (56) [M^+], 130 (100), 102 (24).

***N*-*n*-Butyl-4-anisidine**: Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, ^3J(H,H) = 8.9 Hz, 2H), 6.51 (d, ^3J(H,H) = 8.9 Hz, 2H), 3.22 (br s, 1H), 3.68 (s, 3H), 2.99 (t, ^3J(H,H) = 7.1 Hz, 2H), 1.52 (m, 2H), 1.37 ppm (m, 2H), 0.90 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.4, 143.4, 115.3, 114.4, 56.2, 45.1, 32.2, 20.8, 14.4 ppm; MS (EI, 70 eV): *m*/*z* (%): 179 (55) [M^+], 136 (100).

***N*-(4-Methoxyphenyl)-*N*-methylaniline**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (m, 2H), 7.49 (d, ^3J(H,H) = 9.1 Hz, 2H), 7.29 (d, ^3J(H,H) = 8.9 Hz, 2H), 7.19 (m, 3H), 4.18 (s, 3H), 3.65 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.8, 150.3, 142.7, 129.5, 126.7, 118.9, 116.3, 115.3, 55.9, 41.0 ppm; MS (EI, 70 eV): *m*/*z* (%): 213 (31) [M^+], 198 (100), 77 (12).

***N*-Methyl-*N*-[4-(trifluoromethyl)phenyl]aniline**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 4H), 7.48 (m, 3H), 7.13 (d, ^3J(H,H) = 8.7 Hz, 2H), 3.62 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.0, 148.2, 130.3, 126.7 (q, ^3J(C,F) = 3.8 Hz), 125.8, 125.4, 120.3 (q, ^2J(C,F) = 32.4 Hz), 115.3, 40.6 ppm; ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −60.6 ppm; MS (EI, 70 eV): *m*/*z* (%): 251 (100) [M^+], 77 (24).

***N*-Methyl-*N*-[3-(trifluoromethyl)phenyl]aniline**: Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.13 (m, 3H), 7.04–6.92 (m, 6H), 3.27 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.8, 148.5, 131.8 (q, ^2J(C,F) = 31.8 Hz), 130.1, 129.8, 124.7 (q, ^1J(C,F) = 272 Hz), 124.2, 123.9, 120.8, 116.3 (q, ^3J(C,F) = 3.8 Hz), 113.9 (q, ^3J(C,F) = 3.8 Hz), 40.7 ppm; ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −62.6 ppm; MS (EI, 70 eV): *m*/*z* (%): 251 (100) [M^+], 145 (9), 77 (17); HRMS: calcd for $C_{14}H_{12}NF_3$: 251.09218; found: 251.09357.

***N*-(2,4-Difluorophenyl)-*N*-methylaniline**: Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (m, 3H), 6.80 (m, 2H), 6.69 (m, 1H), 6.59 (m, 2H), 3.14 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.9 (dd, ^1J(C,F) = 147.9 Hz, ^3J(C,F) = 11.4 Hz), 179.4 (dd, ^1J(C,F) = 252.7 Hz, ^3J(C,F) = 12.4 Hz), 132.5 (dd, ^2J(C,F) = 11.4 Hz, ^4J(C,F) = 3.8 Hz), 149.1, 130.4 (dd, ^3J(C,F) = 11.4 Hz, ^3J(C,F) = 9.5 Hz), 129.5, 114.3, 118.8, 112.3 (dd, ^2J(C,F) = 21.9 Hz, ^4J(C,F) = 3.8 Hz), 105.7 (dd, ^2J(C,F) = 26.7 Hz, ^2J(C,F) = 24.7 Hz), 39.3 ppm; ^{19}F NMR (235.4 MHz, $CDCl_3$): δ = −112.6, −115.6 ppm; IR (Nujol): $\tilde{\nu}$ = 3064.7, 2926.7, 2616.1, 1600.2, 1508.5, 1287.3, 1259.8, 1139.9, 965.5, 875.6, 715.0, 692.1 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 219 (100) [M^+], 203 (15), 178 (7), 140 (13), 77 (12); HRMS: calcd for $C_{13}H_{11}NF_2$: 219.08595; found: 219.08524.

***N*-(2-Pyridyl)morpholine**: Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2H), 6.57 (m, 2H), 3.74 (m, 4H), 3.41 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 148.4, 137.9, 114.2, 107.4, 67.2, 46.0 ppm; MS (EI, 70 eV): *m*/*z* (%): 164 (50) [M^+], 133 (66), 107 (44), 79 (100).

***N*-(2-Pyridyl)-2-toluidine**: White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (m, 1H), 7.36 (m, 2H), 7.18–6.55 (m, 5H), 6.34 (br s, 1H), 2.20 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.2, 148.9, 138.9, 138.1, 131.8, 131.5, 127.2, 124.8, 123.3, 115.6, 107.9, 18.4 ppm; MS (EI, 70 eV): *m*/*z* (%): 184 (38) [M^+], 169 (100), 91 (13), 78 (11); HRMS: calcd for $C_{12}H_{12}N_2$: 184.10005; found: 184.09990.

***N*-Benzyl-*N*′-(2-pyridyl)piperazine**: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (m, 1H), 7.37 (m, 1H), 7.29–7.17 (m, 5H), 6.53 (m, 2H), 3.48 (s, 2H), 3.46 (m, 4H), 2.74–2.49 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 148.4, 138.4, 137.8, 129.6, 128.7, 127.6, 113.6, 107.4, 63.6, 53.4, 45.6; MS (EI, 70 eV): *m*/*z* (%): 253 (25) [M^+], 159 (27), 146 (39), 107 (100), 91 (64), 78 (17).

***N*-(6-Methoxy-2-pyridyl)morpholine**: Light brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (t, ^3J(H,H) = 7.9 Hz, 1H), 6.12 (m, 2H), 3.86 (s, 3H), 3.80 (m, 4H), 3.47 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5, 158.8, 140.5, 99.3, 99.2, 67.1, 53.4, 46.0 ppm; IR (Nujol): $\tilde{\nu}$ = 2964.2, 2893.5, 2852.7, 1590.9, 1444.6, 1414.1, 1264.1, 1239.0, 1033.0, 985.8, 780.5 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 194 (63) [M^+], 137 (31), 109 (100); HRMS: calcd for $C_{10}H_{14}N_2O_2$: 194.10553; found: 194.10446.

***N*-Benzyl-*N*′-(2-quinolyl)piperazine**: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, ^3J(H,H) = 9.1 Hz, 1H), 7.61 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.50 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.45 (m, 1H), 7.21 (m, 6H), 6.87 (d, ^3J(H,H) = 9.3 Hz, 1H), 3.68 (t, ^3J(H,H) = 5.1 Hz, 4H), 3.49 (s, 2H), 2.51 ppm (t, ^3J(H,H) = 5.1 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 148.3, 137.8, 129.9, 129.7, 128.7, 127.6, 127.0, 123.5, 122.7, 109.9, 63.6, 53.5, 44.5 ppm; MS (EI, 70 eV): *m*/*z* (%): 303 (11) [M^+], 157 (100), 128 (18), 91 (32).

***N*-Methyl-*N*-(3-pyridyl)aniline**: Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, $^4J(H,H) = 2.6$ Hz, 1H), 8.02 (m, 1H), 7.18 (m, 2H), 7.10 (m, 1H), 6.97 (m, 4H), 3.19 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 148.3$, 145.5, 141.6, 130.0, 128.7, 125.1, 123.8, 123.7, 122.8, 40.4 ppm; MS (EI, 70 eV): *m*/*z* (%): 184 (100) [M^+], 168 (19), 77 (20).

***N*-Methyl-*N*-phenyl-3-(2-hydroxyethyl)aniline**: Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.6$ (m, 2H), 7.5 (m, 1H), 7.36 (m, 2H), 7.29 (m, 1H), 7.2 (m, 2H), 7.13 (m, 1H), 4.14 (t, $^3J(H,H) = 6.54$ Hz, 2H), 3.63 (s, 3H), 3.12 (t, $^3J(H,H) = 6.54$ Hz, 2H), 1.95 ppm (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 149.38$, 149.04, 139.68, 129.43, 129.36, 121.75, 121.69, 121.02, 120.61, 118.21, 63.73, 40.39, 39.42 ppm; IR (neat): $\tilde{\nu} =$ 3355.2, 3026.8, 2937.1, 2874.1, 1593.9, 1582.6, 1494.9, 1345.6, 1258, 1045.5, 992.7, 874.2, 752.3, 696.6, 599.1, 571.5 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 227 (100) [M^+], 196 (19), 181 (23), 167 (8), 105 (11), 91 (17), 77 (17); HRMS: calcd for $C_{15}H_{18}NO$: 228.13884; found: 228.13979.

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