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# Biphenyl sulfonic acid ligands for catalytic C-N cross coupling of aryl halides with anilines and secondary amines

Bärbel Wittel[a], Till Vogel[a], Heiko Scharl[a], Sven Nerdinger[b], Bernd Lehnemann[b], Andreas Meudt[b], Victor Snieckus[a,*]

[a] Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, ON K7L 3N6, Canada
[b] Archimica GmbH, Industriepark Höchst, Building D569, D-65926 Frankfurt am Main, Germany

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ABSTRACT

The use of two biphenyl sulfonic acid ligands for the catalytic C-N cross coupling of aryl halides with anilines, 3-aminopyridine, and secondary amines is reported. Our results represent a significant improvement compared to state of the art methods especially with regards to the removal of palladium.

## 1. Introduction

Ligands are increasingly recognized as the crucial components in transition metal catalyzed cross coupling reactions. The evolving catalogue of ligands arising from academic laboratories and commercial sources lacks systematization and appreciation of their potential success or failure owing to an as yet weak and incomplete mechanistic perspective of the cross coupling reactions.[1–5] For the C-N coupling reaction, an array of ligands including P(o-tolyl)$_3$,[6,7] BINAP,[8–10] DPPF,[11,7] ferrocenyl,[12,13] Josiphos,[14,15] Xantphos, 1[6,17,18] biphenyl,[19,20] and *N*-heterocyclic carbene[21,22] have been successfully tested and applied in new synthetic methodologies. Although, the original contributions of Kunz[23] and Herrmann[24] introduced the TPPTS and BINAS ligands respectively over a decade ago, these classes have received limited development[25,16,26,27,24,28] in spite of their robust nature and water solubility which are of special significance in large-scale and industrial processes.[25,29] [These ligands are generally used with $Pd_2(dba)_3$[10], $Pd(dba)_2$[30] and $Pd(OAc)_2$[31,9,10] palladium sources] (Fig. 1).

## 2. Results and discussion

The C-N cross coupling reaction, increasingly named the Buchwald-Hartwig protocol, has developed into a major component of the synthetic chemist's repertoire.[32] Many of the above catalyst-ligand systems, in combination with NaO*t*Bu[35], lithium hexamethyldisilazide (LiHMDS)[33,34], and $Cs_2CO_3$[9] have found wide application in C-N coupling chemistry. Among C-N coupled products, diarylamines and aryl amines occupy a significant position as compounds of biological and material science interest.[35–38] Herein we report on the synthesis of sulfonic acid ligands **3** and **4** and their use in the Pd-catalyzed C-N cross coupling reaction of aryl bromides and aryl chlorides with anilines, 3-aminopyridine, and cyclic secondary amines. To the best of our knowledge, there has been no reports on the use of sulfonated ligands in palladium-catalyzed C-N coupling reactions (Fig. 2).

The preparation of ligands **3b** (2′-dicyclohexylphosphanyl-6-hydroxy-biphenyl-3-sulfonic acid) and **4b** (2, 2′-dicyclohexylphosphanyl-6-methoxy-biphenyl-3-sulfonic acid) follows convenient, three-step, multi-gram scalable procedures from commercial 2-hydroxybiphenyl and 2-bromoanisole respectively in moderate to good overall yields using mainly classical methods and inexpensive inorganic and Grignard reagents.[25,39–42] The structure of ligand **4b** was confirmed unambiguously by X-ray crystallography.

The most frequently used Pd and base sources for the Buchwald-Hartwig amination, [*inter alia* $Pd_2(dba)_3$,[10] $Pd(dba)_2$,[32] $Pd(OAc)_2$[35,9,10] and NaO*t*Bu,[35] lithium hexamethyldisilazide (LiHMDS),[35,36] $Cs_2CO_3$[9]] were considered for this investigation. High conversions were achieved using diglyme as solvent (Table 1, entries 1 and 4). Extending the addition time did not improve the yields (runs 7 and 3). A good level of conversion was found in $^t$BuOH as well (entries 2 and 5) but slightly lower compared to diglyme. Using NaO*t*Bu as base and diglyme as a solvent, the highest conversion was established (entry 7). Alternatively, using KO*t*Bu, NaOH and KOH as bases, relatively good conversion rates were observed (entries 8, 12 and 13).

Based on these results, the optimum conditions ($Pd(OAc)_2$/NaO*t*Bu/

* Corresponding author.
*E-mail address:* baderadm@chem.queensu.ca (V. Snieckus).

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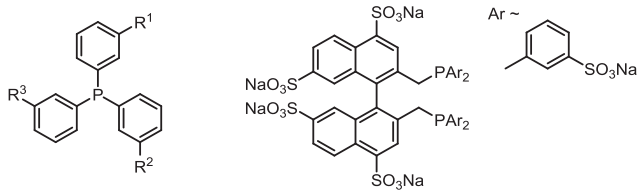



**1a** [25] TPPMS: $R^1 = SO_3H$, $R^2$, $R^3 = H$
**1b** [25] TPPDS: $R^1$, $R^2 = SO_3H$, $R^3 = H$
**1c** [23,25] TPPTS: $R^1$, $R^2$, $R^3 = SO_3H$

**2** [24] BINAS

**Fig. 1.** Some phosphine ligands: TPPMS, TPPDS, TPPTS und BINAS.

diglyme/120 °C) for both ligands **3b** and **4** in coupling reactions were applied for coupling of aryl bromides and chlorides with a diverse series of primary aromatic, pyridyl, and cyclic secondary amines. The results of the scope of the reaction are summarized in Table 2 which merit brief commentary. Although long reaction times are required for many substrates (e.g. entries 1, 6, and 11), excellent conversions were observed using 1.2 equiv of amine with no evidence for homo and diaryl coupling side reactions, whereas in many reported C-N coupling reactions, an excess of amine is used.[32] Thus, 4-bromotoluene underwent smooth coupling with unprotected 3-hydroxyaniline and 3-aminopyridine (entries 1 and 2) to give high conversions albeit with difficulties in isolation. Using 3-aminopyridine as partner (entries 3 and 4), both 2-bromo and 2-chloro-toluenes afforded coupling products also in high conversions indicative of parallel effectiveness of bromines and chlorides under the same conditions and lack of a minor *ortho*-methyl steric effect. The opposite cross coupling combination, halopyridine with arylamine, has been documented.[32] Likewise, in the case of coupling of substrates bearing strong cyano EWGs with piperazine partner (entries 5 and 6), high conversions to products were achieved. No 2:1 coupling products were detected by GC-MS analysis.[29] A fluoro-bromotoluene coupling with aniline afforded a fluorinated diphenylamine (entry 7). As expected,[9,32,10] strong methoxy EDG group containing aryl bromides (entries 8 and 9) and aryl chlorides (entries 10 and 11) were effective coupling partners for anilines. In the case of coupling of 3-chloroanisole (**27**) with *N*-methylaniline (**28**) (entry 10), complete conversion was observed and the pure product (**29**) was isolated in quantitative yield after simple filtration of the reaction mixture.

Extension to halonaphthalene derivatives is exemplified by the cross coupling of 1-bromonaphthalenes with 2,3-dimethylaniline, 4-cyanoaniline, *N*-methylaniline, and morpholine partners (entries 12, 13, 15 and 16) and the apparent equal facility of the reaction using 1-chloronaphthalene (entry 14). Parallel results were obtained in the coupling reactions of 2-bromonaphthalene with anilines and morpholine (entries 17–20). Comparison of entries 19 and 20 demonstrates that the relative effectiveness of ligands **3** and **4** both in time of reaction and yield favours the latter ligand. The amount of ligand and $Pd(OAc)_2$ can be lowered to 1 mol% without loss of effectivity as shown by entry 21. A comparison of ligand **3b** to its non-sulfonated version **3a** shows a much higher conversion rate in favour of **3** (entries 22 and 23) within the same time. While the small scale experiments were processed using column chromatography, the large scale reactions in multi g-scale was processed by extractive workup only thus suggesting facility for industrial application (entries 12 and 13). Repeating the reaction as shown in entry 13 on the same scale but work-up using column chromatograph instead of aqueous extraction gave a lower yield (53%) of product. Selected products analyzed by ICP-MS and ICP-OES for Pd-content from several reactions were shown to contain as low as 3.2 ppm Pd, e.g. for entry 12.

## 3. Summary and conclusions

In conclusion, the use of sulfonylated ligands **3b** and **4b** for efficient Pd-catalyzed C-N cross coupling reactions of aryl bromides and aryl chlorides with a selection of anilines, 3-aminopyridine and cyclic secondary amines has been demonstrated. The availability of **3b** and **4** on multi gram scale by simple synthesis, the convenient, non-chromatography dependent, large-scale processing, and the low Pd-content of derived product bode well for the broader utility of our C-N coupling protocol. In addition, potential further design and implementation of sulfonated ligands in cross coupling regimens may be anticipated.

## 4. Experimental

All reactions were carried out under an argon atmosphere in oven-dried glassware. Anhydrous diglyme was purchased from Aldrich and was used without further purification. All amines were obtained from commercial sources and were used without further purification. Palladium(II)chloride and sodium *tert*-butoxide were obtained from Aldrich and used without further purification. Preparative flash column chromatography was performed on Silica-P Flash Silica Gel from Silicycle Chemical Division silica gel. TLC was carried out on aluminium sheets 40–63 µm, 500 $m^2/g$ $F_{254}$ purchased from Merck KGaA, $^1H$ and $^{13}C$ NMR spectra were recorded using a Bruker Avance-400 or Avance-300 spectrometer operating at 400 MHz and 300 MHz respectively ($^1H$ frequency, corresponding $^{13}C$ frequencies are 100 MHz and 75 MHz). In the $^13C$ NMR spectra, signals corresponding to CH, $CH_2$, or Me groups are assigned from DEPT. IR were measured on an Avatar 360 FT-IR, Mass spectra were recorded on a Micromass 70-250S double focusing mass spectrometer (EI) or Waters ZQ Single Quad mass spectrometer (ESI). Pd-Values were measured after $HNO_3$ and $H_2SO_4$ pulping in the microwave using the ICP-MS and ICP-OES methods. A crystal of the compound (colorless, block-shaped, size 0.30 × 0.24 × 0.20 mm) was mounted on a glass fiber with grease and cooled to −93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å), operating at 50 kV and 30 mA over 2θ ranges of 3.72–51.96°. No significant decay was observed during the data collection.

Data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package[43] Data collection: APEX2 (Bruker, 2006); cell refinement: SAINT (Bruker, 2005); data reduction: SAINT (Bruker, 2005); structure solution: XPREP (Bruker, 2005) and SHELXTL (Bruker, 2000); structure refinement: SHELXTL; molecular graphics: SHELXTL; publication materials: SHELXTL. Neutral atom scattering factors were taken from Cromer and Waber.[44] The crystal is orthorhombic space group $P2_12_12_1$, based on the systematic absences, E statistics and successful refinement of the structure. The structure was solved by direct methods. Full-matrix least-square refinements minimizing the function $\Sigma w (F_o^2 – F_c^2)^2$ were applied to the compound. All non-hydrogen atoms were refined anisotropically. CCDC 1,849,107 (**4b**), CCDC 1,849,106 (**13**) and CCDC 1,849,105 (**39**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

### 4.1. 2-Hydroxy-2′-dicyclohexylphosphinobiphenyl-5-sulfonic acid (3b)

2-Hydroxy-2′-dicyclohexylphosphinobiphenyl **3a** (1.10 g, 3.0 mmol) was cooled in an ice bath and purged with argon. Conc. $H_2SO_4$ (2 mL) was added slowly via syringe. After warming to rt, the suspension was stirred for 2 h until all of the solid had dissolved to give a homogeneous, slightly brown solution which was cooled in an ice bath and quenched by addition of crushed ice. The suspension was treated with conc. NaOH solution until the precipitate had completely dissolved. The resulting solution was diluted with water (75 mL) and acidified with 1 N $H_2SO_4$. The precipitate was collected on a glass filter and washed with water until the filtrate was neutral as observed by litmus-paper. The colorless residue was washed with methanol and dried under vacuum to give 2-Hydroxy-2′-dicyclohexylphosphinobiphenyl-5-sulfonic acid

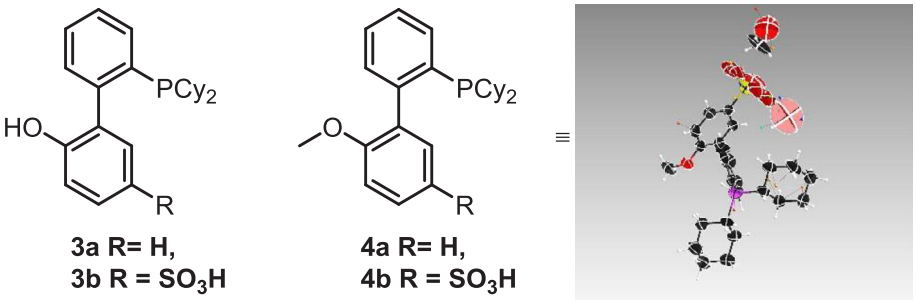



**Fig. 2.** Sulfonated ligands **3b** and **4b.**

(1.09 g, 2.45 mmol, 82%) as colorless crystals, mp (free acid) 285–295 °C (decomp.) (hot MeOH). IR (KBr) (free acid): υ = 3445, 3062, 2946, 2857, 1604, 1415, 1233, 1168, 1112, 1029, 1012, 832, 675, 593 $cm^{-1}$. $^1H$ NMR ($D_2O$/NaOH, 400 MHz): $\delta$ = 0.90–1.20 (m, 10*H*), 1.44–1.73 (m, 10*H*), 1.78–1.85 (m, 2H), 6.53 (d, *J* = 8.2 Hz, 1H), 7.21–7.30 (m, 3H), 7.34 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 5.3 Hz, 1H). $^{13}C$ NMR ($D_2O$/NaOH, 100 MHz): $\delta$ = 26.0, 26.1, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 29.2, 29.3, 29.5, 29.8, 30.1 and 30.3 (14,15,16-$CH_2$), 33.2 (d, *J* = 8 Hz, 1C), 34.2 (d, *J* = 9 Hz, 1C), 119.0 (11-C), 125.0 (9-C), 126.3 (4-CH), 128.6 (2-CH), 129.6 (3-CH), 131.5 (d, *J* = 5 Hz, 8-CH), 132.0 (d, *J* = 7 Hz, 1-C), 132.7 (5-CH), 134.3 (d, *J* = 9 Hz, 6-C), 148.6 (d, *J* = 27 Hz, 7-C), 168.3 (12-C). $^{31}P$ NMR ($D_2O$/NaOH, 162 MHz): δ = −10.6. MS (Maldi-TOF): *m/z* = 485 (1 0 0) [$M^+$ + K], 367 (65). HRMS (Maldi-TOF): *m/z* = $C_{24}H_{31}PO_4S$ calcd. 485.1318; found 485.1314.

### 4.2. 2, 2′-dicyclohexylphosphanyl-6-methoxy-biphenyl-3-sulfonic acid (4b)

2′-Methoxy-2-dicyclohexylphosphinobiphenyl[41] (1.03 g, 2.7 mmol) was cooled in an ice bath to 0 °C under argon. Conc $H_2SO_4$ (2.0 mL) was added via syringe and the reaction mixture was stirred 12 h at rt. The reactions mixture was cooled to 0 °C and quenched with $H_2O$ (4 mL) and neutralized with dil. NaOH solution. The aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The organic phases were combined, dried ($Na_2SO_4$), subjected to filtration and the filtrate was evaporated to dryness in vacuo. The crude product was purified by flash column chromatography $CHCl_3$ and $CHCl_3$-MeOH (10:1) eluent to yield 1.22 g (0.265 mmol, 98%) of 2, 2′-dicyclohexylphosphanyl-6-methoxy-biphenyl-3-sulfonic acid (**4b**) as colorless crystals, mp > 250 °C ($CHCl_3$-MeOH). Crystals suitable for X-ray were grown from a saturated solution in methanol by slow evaporation. IR (neat) υ = 3583, 2929, 1738, 1591, 1495, 1456, 1347, 1274, 1213, 1168, 1126, 1045, 691 $cm^{-1}$. $^1H$ NMR (MeOH/NaOH, 400 MHz): $\delta$ = 0.92–1.36 (m, 10*H*), 1.52–1.69 (m, 11*H*), 1.96 (m, 1 H), 3.76 (s, 3 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.16 (d, *J* = 4.2 Hz, 1 H), 7.39 (m, 2 H), 7.57 (s, 2 H), 7.86 (m, 1 H). $^{13}C$ NMR (MeOH/NaOH, 100 MHz): $\delta$ = 27.65 (d, *J* = 16.7 Hz, 2 $CH_2$), 28.25 (d, *J* = 15.4 Hz, 2 $CH_2$), 28.36 (d, *J* = 16.2 Hz, 2 $CH_2$), 30.05 (d, *J* = 6.0 Hz, 1 $CH_2$), 31.14 (d, *J* = 12.1 Hz, 1 $CH_2$), 31.46 (d, *J* = 17.5 Hz, 1 $CH_2$), 32.09 (d, *J* = 17.4 Hz, 1 $CH_2$), 35.14 (d, *J* = 11.3 Hz, 1 CH), 36.64 (d, *J* = 13.8 Hz, 1 CH), 55.90 (s, 1 $CH_3$), 110.71 (s, 1 CH), 127.89 (s, 1 CH), 129.59 (s, 1 CH), 130.75 (s, 1 CH), 131.41 (s, 1 CH), 131.47 (s, 1 CH), 133.08 (d, *J* = 6.8 Hz, 1 C), 133.47 (s, 1 CH), 136.38 (d, *J* = 17.7 Hz, 1 C), 137.38 (s, 1 C), 147.74 (s, 1 C), 159.46 (s, 1 C). $^{31}P$ NMR (MeOH/NaOH, 162 MHz): δ = −10.54. MS (Maldi-TOF): *m/z* = 483 (1 0 0) [$M^+$ + Na], 461 (42) [$M^+$ + H]. HRMS (Maldi-TOF) $C_{25}H_{33}PO_4S$ calcd. 461.1915; found 461.1907.

### 4.3. 4-(Naphthalen-1-yl-amino)-benzonitrile (9)

NaO*t*Bu (4.42 g, 46.0 mmol), ligand **3b** (103 mg, 0.23 mmol), Pd $(OAc)_2$ (52 mg, 0.23 mmol) and 4-aminobenzonitrile (3.53 g, 30 mmol) were sequentially added to a dry, round-bottom flask under Ar. Diglyme (70 mL) was added and, after 15 min, the resulting suspension was treated with 1-bromonaphthalene (4.76 g, 3.2 mL, 23 mmol). After being stirred at 120 °C for 15 h, the reaction mixture was cooled. Passed through silica gel and the residue was washed with ether. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/ethyl acetate 4:1) to give 4.3 g (77%) of compound **9** as pale yellow crystals, mp. 132–134 °C (hexane/ethyl acetate). IR (neat): υ = 3328, 2210, 1592, 1496, 1397, 1330, 1215, 1167, 1126, 820, 801, 773 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.04 (b, 1H), 6.63 (m, 2H), 7.26–7.41 (m, 6H), 7.57 (m, 1H), 7.75 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 100.95 (s, 1C), 114.53 (d, 1C), 115.23 (d, 1C), 119.49 (s, 1C), 121.49 (d, 1C), 122.21 (d, 1C), 125.86 (d, 1C), 126.318 (d, 1C), 126. 52 (d, 1C), 126.79 (d, 1C), 128.65 (d, 1C), 129.43 (s, 1C), 133.73 (d, 1C), 134.75 (s, 1C), 135.57 (s, 1C), 149.91 (s, 1C). MS ($EI^+$, 70 eV): *m/z* = 244 (1 0 0) [$M^+$], 243 (58), 242 (44), 115 (9). HRMS ($EI^+$, 70 eV): *m/z* = $C_{17}H_{12}N_2$ calcd. 244.1000; found 244.0999. Pd-content: 180 ppm

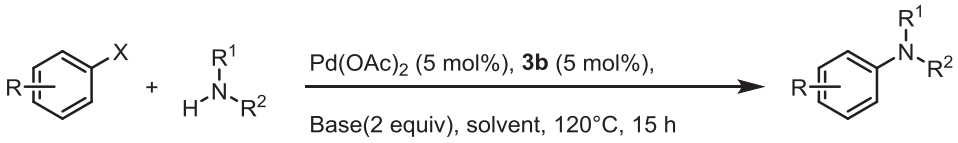
### 4.4. Pyridin-3-yl-p-tolyl-amine (13)

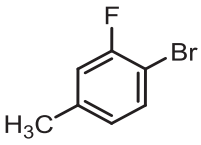
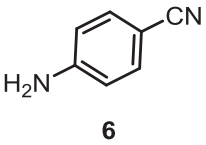
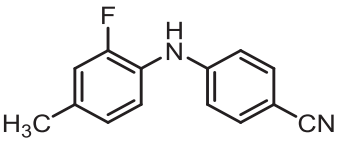
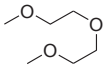
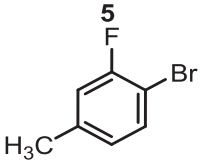
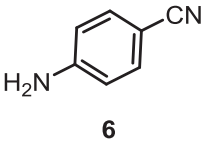
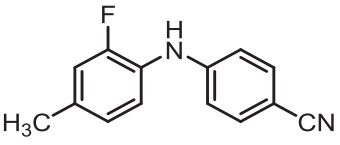
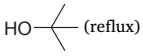
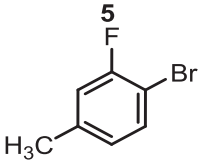
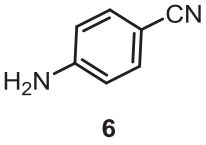
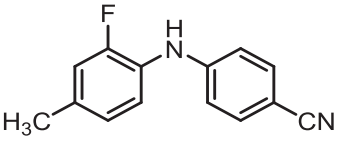
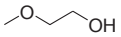
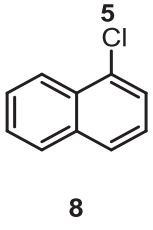
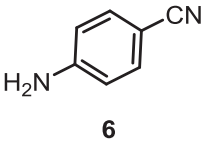
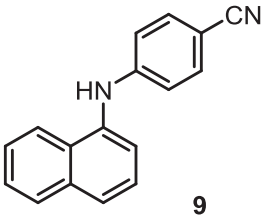
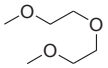
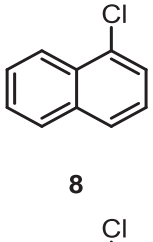
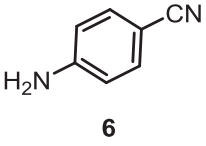
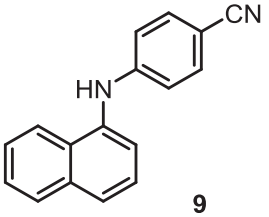
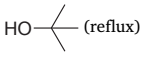
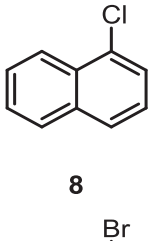
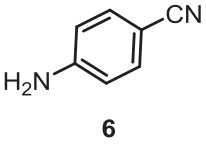
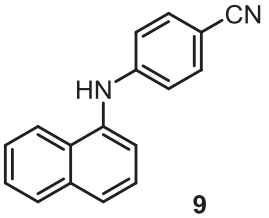
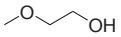
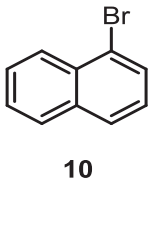
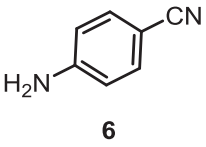
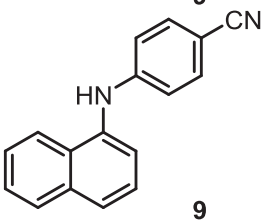
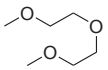
In a dry flask, solid NaO*t*Bu (1.15 g, 12.0 mmol) was stirred under Ar for 12 h at 120 °C, diglyme (18 mL) was added, and the resulting suspension was stirred for 45 min and then were sequentially added 3-aminopyridine (565 mg, 6.0 mmol), 4-bromotoluene (738 µl, 6.0 mmol) and a suspension (2.4 mL) of $Pd(OAc)_2$ (33 mg, 0.15 mmol) and ligand **3b** (68 mg, 0.15 mmol) in diglyme (3 mL). After being stirred for 4 d, the reaction mixture was subjected to filtration, the filtrate was washed with MeOH and the combined filtrate was evaporated to dryness in vacuo. The residue was dissolved in $H_2O$/$CH_2Cl_2$ (150 mL of each), the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were extracted with $H_2O$ (100 mL), dried ($MgSO_4$), subjected to filtration and the filtrate was concentrated to dryness in vacuo. The crude product was recrystallized from ethyl acetate/hexane to give 534 mg (48%) of compound **13** as a yellow brown solid, mp. 92 °C (hexane/EtOAc). IR (KBr): υ = 3265, 3188, 3098, 3046, 2982, 2911, 2357, 2351, 2112, 1591, 1475, 1327, 1114, 812, 702, 644, 618, 496 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.33 (s, 3H), 6.00 (br, 1H), 7.03 (m, 2H), 7.16 (m, 3H), 7.38 (m, 1H), 8.10 (m, 1H), 8.37 (d, *J* = 2.4 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 20.75 (q, 1C), 119.60 (d, 2C), 122.65 (d, 1C), 123.90 (d, 1C), 130.10 (d, 2C), 132.29 (s, 1C), 138.61 (d, 1C), 140.30 (d, 1C), 141.00 (s, 1C), 152.42 (s, 1C). MS ($EI^+$): *m/z* = 184 (1 0 0) [$M^+$], 169 (7), 91 (9). HRMS ($EI^+$): *m/z* = $C_{12}H_{12}N_2$calcd. 184.1000; found 184.0997.

### 4.5. Pyridin-3-yl-o-tolyl-amine (15)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (9 mL) was added, and after 30 min, the resulting suspension was sequentially treated with 3-aminopyridine (282 mg, 3.0 mmol), 2-chlorotoluene

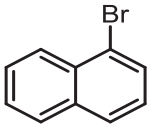
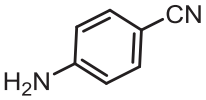
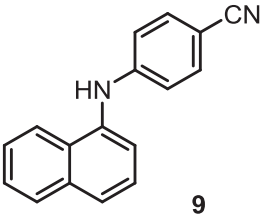
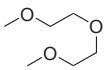
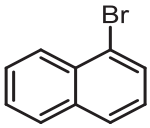
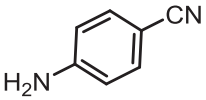
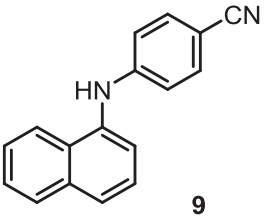
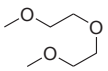
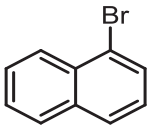
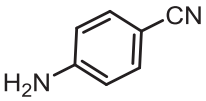
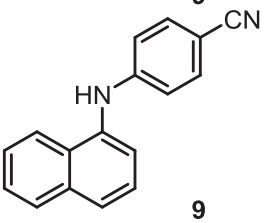
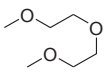
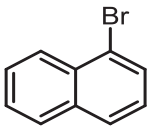
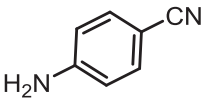
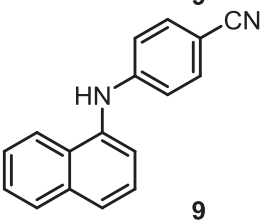
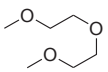
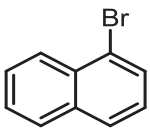
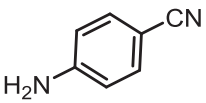
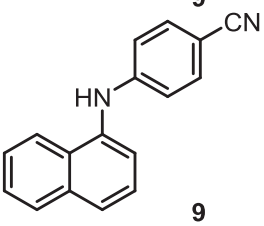
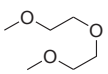
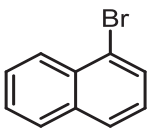
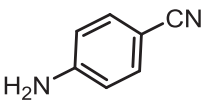
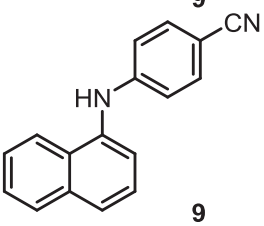
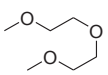
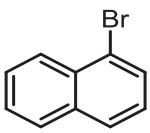
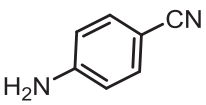
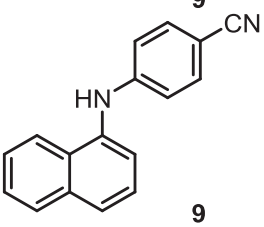
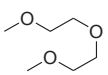
**Table 1**
Optimization of the C-N Cross Coupling Reaction of ArBr and ArCl with Anilines and Secondary Amines using Ligand **3b**.




| Entry | Aryl halide | Amine | Product | Ligand | Base (2 equiv.) | Solvent | Conversion[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **5** |  **6** |  **7** | **3b** | NaO*t*Bu |  | 93 |
| 2 |  **5** |  **6** |  **7** | **3b** | NaO*t*Bu |  | 62 |
| 3 |  **5** |  **6** |  **7** | **3b** | NaO*t*Bu |  | 0 |
| 4 |  **5** **8** |  **6** |  **7** **9** | **3b** | NaO*t*Bu |  | 94 |
| 5 |  **8** |  **6** |  **9** | **3b** | NaO*t*Bu |  | 72 |
| 6 |  **8** |  **6** |  **9** | **3b** | NaO*t*Bu |  | 0 |
| 7 |  **10** |  **6** |  **9** | **3b** | NaO*t*Bu |  | 86 |

(*continued on next page*)

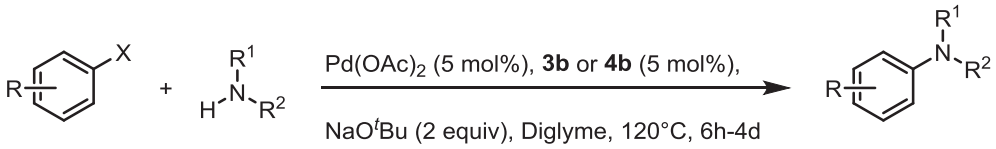
**Table 1** (*continued*)

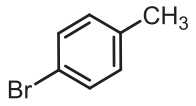
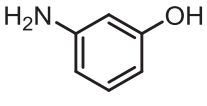
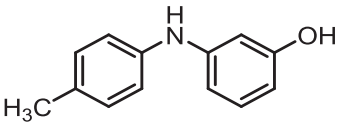
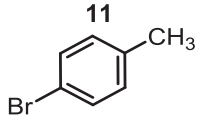
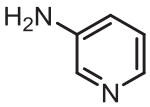
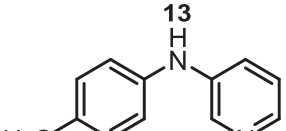
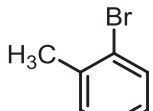
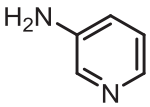
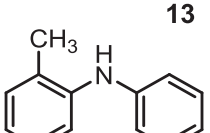
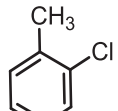
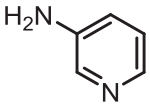
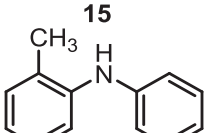
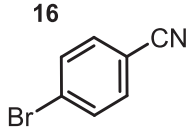
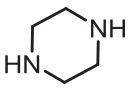
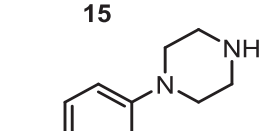
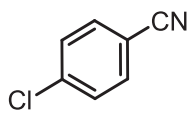
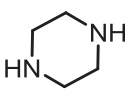
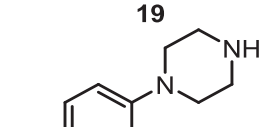
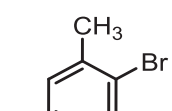
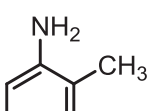
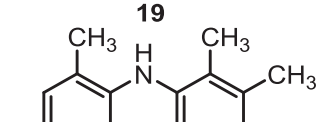
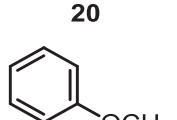
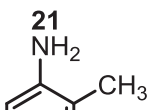
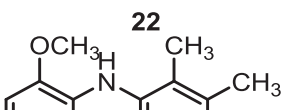
| Entry | Aryl halide | Amine | Product | Ligand | Base (2 equiv.) | Solvent | Conversion[a] (%) |
|---|---|---|---|---|---|---|---|
| 8 |  **10** |  **6** |  **9** | **3b** | KO*t*Bu |  | 66 |
| 9 |  **10** |  **6** |  **9** | **3b** | $K_3PO_4$ |  | 13 |
| 10 |  **10** |  **6** |  **9** | **3b** | NaOMe |  | 43 |
| 11 |  **10** |  **6** |  **9** | **3b** | LiOH |  | 0 |
| 12 |  **10** |  **6** |  **9** | **3b** | NaOH |  | 44 |
| 13 |  **10** |  **6** |  **9** | **3b** | KOH |  | 67 |
| 14 |  **10** |  **6** |  **9** | **3b** | $Cs_2CO3$ |  | 16 |

[a] Conversion based on GC–MS analysis.

(351 µl, 3.0 mmol) and a suspension (1.2 mL) of $Pd(OAc)_2$ (33 mg, 0.15 mmol) and ligand **3b** (68 mg, 0.15 mmol) in diglyme (3 mL). After being stirred at 120 °C for 4 d, the reaction mixture was subjected to filtration and the filter cake was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 8:1, 6:1, 4:1, 2:1 eluent) to give 258 mg (47%) of compound **15** as a yellow–brown oil. IR (neat): υ = 3247, 3026, 1576, 1521, 1484, 1459, 1408, 1315, 1238, 1112, 1045, 796, 747, 707 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.06 (s, 3H), 6.17 (s, 1H), 6.81 (m, 1H), 6.90 (m, 1H), 6.99 (m, 4H), 7.88 (m, 1H), 8.10 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 18.22 (q, 1C), 120.51 (d, 1C), 122.50 (d, 1C), 123.42 (d, 1C), 123.83 (d, 1C),

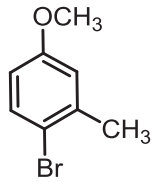
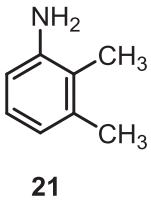
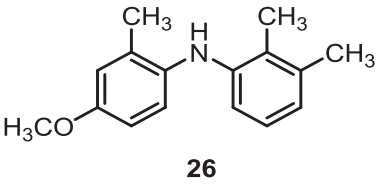
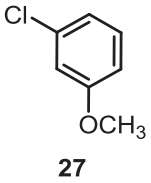
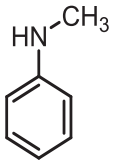
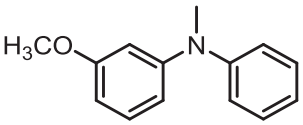
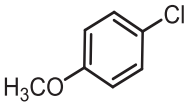
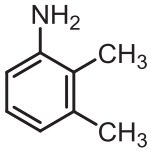
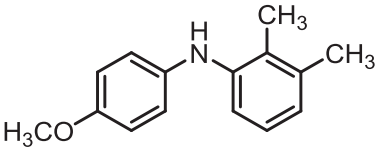
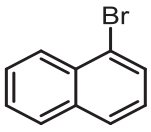
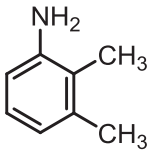
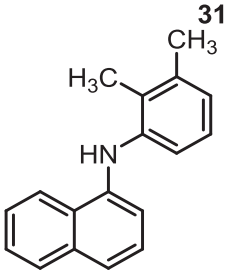
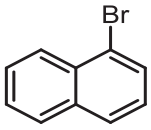
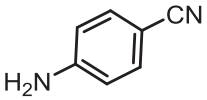
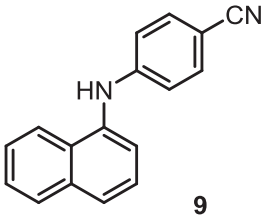
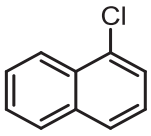
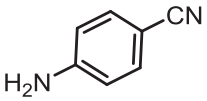
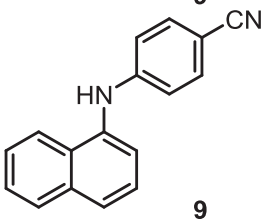
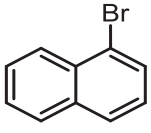
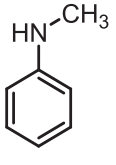
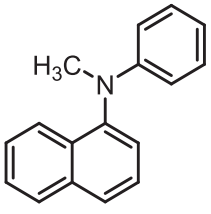
**Table 2**
Optimization of the C-N Cross Coupling Reaction of ArBr and ArCl with Anilines and Secondary Amines using Ligands **3b** and **4b**.




| Entry | Aryl halide | Amine | Product | Ligand | Reaction time | Conversion[a] (%) | Isolated yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **11** |  **12** |  **13** | **3b** | 15 h | 95 | 95[c] |
| 2 |  **11** |  **12** |  **13** | **3b** | 4d | 98 | 48[x] |
| 3 |  **14** |  **12** |  **15** | **3b** | 1 d | 94 | 24 |
| 4 |  **16** |  **12** |  **15** | **3b** | 4 d | 94 | 47 |
| 5 |  **17** |  **18** |  **19** | **3b** | 6 h | 98 | 98[c] |
| 6 |  **20** |  **18** |  **19** | **3b** | 2 d | 91 | 91[c] |
| 7 |  **20** |  **21** |  **22** | **3b** | 15 h | 93 | 93[c] |
| 8 |  **23** |  **21** |  **24** | **4b** | 2 d | -[d] | 27 |

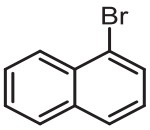
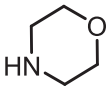
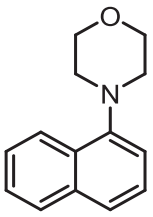
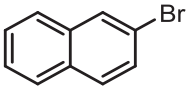
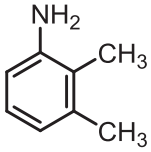
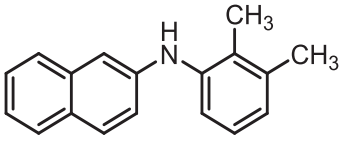
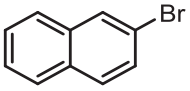
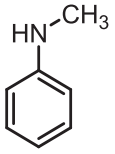
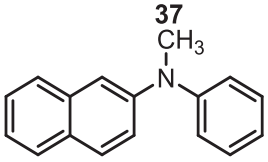
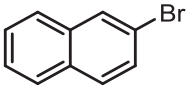
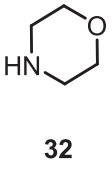
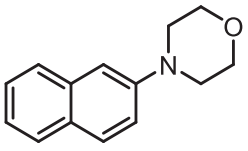
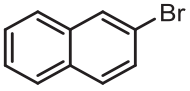
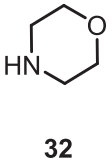
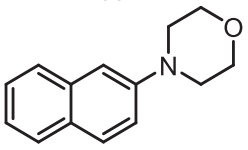
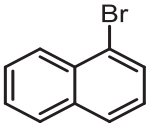
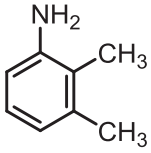
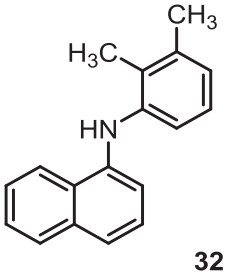
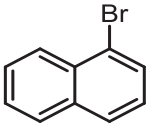
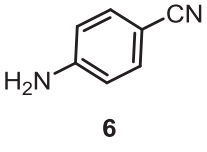
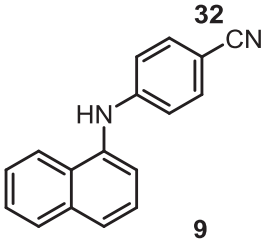
(*continued on next page*)

**Table 2** (*continued*)

| Entry | Aryl halide | Amine | Product | Ligand | Reaction time | Conversion[a] (%) | Isolated yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 9[f] |  **25** |  **21** |  **26** | **4b** | 15 h | 100 | 53 |
| 10 |  **27** |  **28** |  **29** | **4b** | 3 d | 100 | quant[e] |
| 11 |  **30** |  **21** |  **31** | **3b** | 14 h | 87 | 87[c] |
| 12 |  **10** |  **21** |  **32** | **3b** | 14 h | – | 80 |
| 13 |  **10** |  **6** |  **9** | **3b** | 15 h | – | 77 |
| 14 |  **8** |  **6** |  **9** | **3b** | 15 h | 95 | 95[c] |
| 15 |  **10** |  **28** |  **33** | **4b** | 1 d | 89 | 72 |

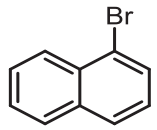
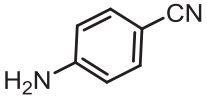
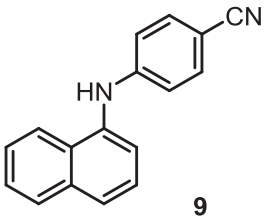
(*continued on next page*)

**Table 2** (*continued*)

| Entry | Aryl halide | Amine | Product | Ligand | Reaction time | Conversion[a] (%) | Isolated yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 16 |  **10** |  **34** |  **35** | **4b** | 1 d | 94 | 85 |
| 17 |  **36** |  **21** |  **37** | **4b** | 4 d | 95 | 95[c] |
| 18 |  **36** |  **28** |  **38** | **4b** | 1 d | 95 | 78 |
| 19 |  **36** |  **32** |  **39** | **3b** | 2 d | 65 | 56[x] |
| 20 |  **36** |  **32** |  **39** | **4b** | 1 d | -[c] | 75 |
| 21 |  **10** |  **21** |  | **3b (1 mol %)** | 48 h (140 °C) | 94 | 94[c] |
| 22 |  **10** |  **6** |  **9** | **3b (1 mol %)** | 9 h | 89 | 89[c] |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Aryl halide | Amine | Product | Ligand | Reaction time | Conversion[a] (%) | Isolated yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 23 |  **10** |  **6** |  **9** | **3a (1 mol %)** | 9 h | 48 | 48[c] |

[x] Crystal structures of products are deposited at the Cambridge Crystallographic Data Centre.
[a] GC–MS analysis.
[b] Based on products obtained after column chromatography.
[c] Conversion based on GC–MS analysis without isolation.
[d] Not analyzed.
[e] The product was obtained after filtration through silica gel.
[f] T = 100 °C.

126.91 (d, 1C), 130.20 (s, 1C), 131.26 (d, 1C), 139.03 (d, 1C), 140.10 (s, 1C), 140.45 (d, 1C), 141.55 (s, 1C). MS ($EI^+$): *m/z* = 184 (1 0 0) [$M^+$], 183 (38), 169 (10). HRMS ($EI^+$): *m/z* = $C_{12}H_{12}N_2$ calcd. 184.1000; found. 184.1007.

Alternative procedure: NaO*t*Bu (192 mg, 2.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (3 mL) was added, and after 30 min, the resulting suspension was sequentially treated with 3-aminopyridine (104 mg, 1.1 mmol), 2-bromotoluene (120 µl, 1.0 mmol) and a suspension (0.4 mL) of Pd $(OAc)_2$ (33 mg, 0.15 mmol) and ligand **3b** (68 mg, 0.15 mmol) in diglyme (3 mL). After being stirred at 120 °C for 1 d, the reaction mixture was subjected to filtration and the filter cake was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was dissolved in $H_2O/CH_2Cl_2$ (10 mL of each), the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were extracted with $H_2O$ (50 mL), dried ($Na_2SO4$), subjected to filtration and the filtrate was concentrated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 10:1, 8:1, 6:1, 4:1, 2:1 eluent) to give 518 mg (24%) of compound **15** as a yellow oil.

### 4.6. (2,3-Dimethyl-phenyl)-(2-methoxyphenyl)-amine (24)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (9 mL) was added, and after 30 min, the resulting suspension was sequentially treated with 2,3-dimethylaniline (402 µg, 3.3 mmol), 2-bromoanisole (375 µl, 3.0 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4b** (28 mg, 0.15 mmol). After being stirred at 120 °C for 2 d, the reaction mixture was subjected to filtration through silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane) to give 182 mg (27%) of compound **24** as a yellow solid, mp. 46 °C (hexane). IR (neat): υ = 3410, 1939, 1584, 1508, 1465, 1412, 1337, 1297, 1277, 1241, 1214, 1175, 1117, 1030, 740 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.10 (s, 3H), 2.25 (s, 3H), 3.84 (s, 3H), 5.79 (s, 1H), 6.70–6.85 (m, 5H), 6.98 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 13.70 (q, 1C), 20.70 (q, 1C), 55.63 (q, 1C), 110.22 (d, 1C), 113.77 (d, 1C), 118.68 (d, 1C), 119.40 (d, 1C), 120.90 (d, 1C), 124.80 (d, 1C), 125.85 (d, 1C), 129.45 (s, 1C), 134.84 (s, 1C), 137.83 (s, 1C), 140.49 (s, 1C), 147.66 (s, 1C). MS ($EI^+$): *m/z* = 227 (95) [$M^+$], 212 (22), 197 (1 0 0), 194 (29). HRMS ($EI^+$): *m/z* = $C_{15}H_{17}NO$ calcd. 227.1310; found 227.1308.

### 4.7. (2,3-Dimethyl-phenyl)-(4-methoxy-2-methyl-phenyl)-amine (26)

NaO*t*Bu (577 mg, 6.0 mmol), ligand **4b** (28 mg, 0.06 mmol) and $Pd(OAc)_2$ (14 mg, 0.06 mmol) was added to a dry round-bottom flask under Ar. Diglyme (9 mL) was added and the resulting suspension was sequentially treated with 4-bromo-3-methylanisole (423 µl, 3.0 mmol) and 2,3-dimethylaniline (402 µg, 3.3 mmol). After being stirred at 100 °C for 15 h, the reaction mixture was subjected to filtration through silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 15:1) to give 743 mg (53%) of compound **26** as an orange oil. IR (neat): υ = 3403, 3029, 2941, 2859, 2833, 1608, 1588, 1504, 1456, 1281, 1217, 1158, 1119, 1093, 1068, 992, 864, 850, 770, 714 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.27 (s, 3H), 2.31 (s, 3H), 2.42 (s, 3H), 3.88 (s, 3H), 5.07 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.79 (m, 2H), 6.89 (d, *J* = 2.7 Hz, 1H), 7.03 (m, 2H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 13.17 (q, 1C), 18.24 (q, 1C), 20.78 (q, 1C), 55.54 (q, 1C), 111.90 (d, 1C), 113.46 (d, 1C), 116.12 (d, 1C), 121.44 (d, 1C), 123.53 (s, 1C), 124, 01 (d, 1C), 126.04 (d, 1C), 132.84 (s, 1C), 134.92 (s, 1C), 137.27 (s, 1C), 144.05 (s, 1C), 155.82 (s, 1C). MS ($EI^+$): *m/z* = 214 (90) [$M^+$], 226 (1 0 0), 218 (42), 194 (11), 131 (18), 69 (20). HRMS ($EI^+$): *m/z* = $C_{16}H_{19}NO$ calcd. 241.3238; found 241.1472.

### 4.8. Methyl-3-methoxyphenylamine (29)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (7 mL) was added and the resulting suspension was sequentially treated with *N*-methylaniline (306 µg, 3.0 mmol), 3-chloroanisole (365 µl, 3.0 mmol) and a suspension of $Pd(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4b** (28 mg, 0.06 mmol) in diglyme (2 mL). After being stirred at 120 °C for 3 d, the reaction mixture was passed through a bed of silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo to give 638 mg (quant.) of compound **29** as a yellow solid, mp. 67 °C (MeOH). IR (neat): υ = 3058, 3034, 2999, 2938, 2833, 2812, 1591, 1575, 1495, 1456, 1347, 1273, 1214, 1168, 1127, 1094, 1048, 990, 929, 847, 753, 691 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 40.40 (q, 1C), 55.26 (q, 1C), 105.70 (d, 1C), 106.00 (d, 1C), 112.62 (d, 1C), 121.70 (d, 2C), 121.96 (d, 1C), 128.44 (d, 2C), 129.08 (d, 1C), 148.98 (s, 1C), 150.49 (s, 1C), 160.66 (s, 1C). MS ($EI^+$, 70 eV): *m/z* = 213 (1 0 0) [$M^+$], 197 (5), 154 (5). HRMS ($EI^+$, 70 eV): *m/z* = $C_{14}H_{15}NO$ calcd.213.1154; found 213.1155.

### 4.9. (2,3-Dimethylphenyl)-naphthalen-1-yl-amine (32)

NaO*t*Bu (18.3 g, 190 mmol), ligand **3b** (424 mg, 0.95 mmol) and Pd $(OAc)_2$ (213 mg, 0.95 mmol) were added to a dry, round-bottom flask under Ar. Diglyme (290 mL) was added and after 15 min, the resulting suspension was sequentially treated with 2,3-dimethylanilin (13.2 g, 109 mmol) and 1-bromonaphthalene (19.7 g, 95 mmol). After being stirred at 120 °C for 14 h, the reaction mixture was cooled to rt, 750 mLof $H_2O$ was added and the resulting solution was extracted with toluene (3 × 250 mL). The combined organic phases were dried ($Na_2SO_4$), subjected to filtration and the filtrate was concentrated to dryness in vacuo. The resulting brown residue was fractionally distilled using a Kugelrohr apparatus to yield the crude product as red crystals. Recrystallization from hexane gave 18.7 g (80%) of compound **32** as pale red crystals, mp. 58–60 °C (hexane), mp.[45] 68–69 °C (ethanol). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.32 (s, 3H), 2.44 (s, 3H), 5.86 (s, 1H), 6.95 (m, 3H), 7.12 (m, 1H), 7.41 (m, 1H), 7.56 (m, 3H), 7.92 (1H), 8.08 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 13.75 (q, 1C), 20.78 (q, 1C), 113. 40 (d, 1C), 118.72 (d, 1C), 121.37 (d, 1C), 124.45 (d, 1C), 125. 28 (d, 1C), 125.50 (d, 1C), 126.05 (d, 1C), 126.21 (d, 1C), 126.29 (d, 1C), 126.46 (s, 1C), 127.97 (s, 1C), 128.67 (d, 1C), 134.71 (s, 1C), 137.88 (s, 1C), 140.59 (s, 1C), 142.11 (s, 1C). MS (EI$^+$, 70 eV): *m/z* = 247 (1 0 0) [M$^+$], 232 (29), 217 (11). HRMS (EI$^+$, 70 eV): *m/z* = $C_{18}H_{17}N$ calcd. 247.1361; found 247.1373. Pd-content: 3.20 ppm.

### 4.10. Methylnaphthalen-1-yl-phenyl-amine (33)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (7 mL) was added and after 60 min, the resulting suspension was sequentially treated with *N*-methylaniline (306 µl, 3.0 mmol), 1-bromonaphthalene (420 µl, 3.0 mmol) and, after an additional 30 min, a suspension of Pd $(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4** (28 mg, 0.06 mmol) in diglyme (2 mL). After being stirred at 120 °C for 1 d, the reaction mixture was filtered over silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane) to give 506 mg (72%) of compound **33** as a yellow oil. IR (neat): υ = 3088, 3057, 3004, 2935, 2881, 2810, 1712, 1599, 1574, 1498, 1476, 1393, 1339, 1297, 1186, 1139, 1009, 775, 693 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.61 (s, 3H), 6.89 (d, *J* = 8.1 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 7.41 (m, 2H), 7.23 (m, 2H), 7.59–7.72 (m, 2H), 8.00 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ =40.47 (q, 1C), 113.89 (d, 2C), 117.58 (d, 1C), 124.13 (d, 1C), 125.50 (d, 1C), 126.53 (d, 1C), 126.66 (d, 1C), 126.76 (d, 1C), 126.92 (d, 1C), 128.77 (d, 1C), 128.94 (d, 2C), 131.62 (s, 1C), 135.43 (s, 1C), 145.68 (s, 1C), 150.39 (s, 1C).. MS (EI$^+$, 70 eV): *m/z* = 233 (1 0 0)[M$^+$], 217 (40). . HRMS (EI$^+$, 70 eV): *m/z* = $C_{17}H_{15}N$ calcd. 233.1204; found 233.1203.

### 4.11. 4-Naphthalen-1-yl-morpholine (35)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (7mL) was added and after 30 min, the resulting suspension was sequentially treated with morpholine (262 µl, 3.0 mmol), 1-bromonaphthalene (621 mg, 3.0 mmol) and, after an additional 30 min, a suspension of Pd $(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4b** (28 mg, 0.06 mmol) in diglyme (2 mL). After being stirred at 120 °C for 1 d, the reaction mixture was passed through silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 400:1, 300:1, 200:1, 40:1) to give 546 mg (85%) of compound **35** as a yellow solid, mp. 64 °C (hexane/acetone), mp.[46] 83 °C (ethanol). IR (neat): υ = 3049, 2954, 2885, 2820, 1592, 1577, 1452, 1398, 1262, 1257, 1113, 1103, 776 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.16 (s, 4H), 4.02 (t, *J* = 4.4 Hz, 4H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.54 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 8.28 (d, *J* = 7.5 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 53.55 (t, 2C), 67.49 (t, 2C), 114.74 (d, 1C), 123.46 (d, 1C), 123.90 (d, 1C), 125.54 (d, 1C), 125.91 (d, 1C), 125.96 (d, 1C), 128.54 (d, 1C), 128.82 (s, 1C), 134.86 (s, 1C), 149.40 (s, 1C). MS (EI$^+$, 70 eV): *m/z* = 213 (96) [M$^+$], 155 (1 0 0), 127 (37). HRMS (EI$^+$, 70 eV): *m/z* = $C_{14}H_{15}NO$ calcd. 213.1154; found 213.1158.

### 4.12. Methylnaphthalen-2-yl-phenyl-amine (38)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (7mL) was added and after 60 min, the resulting suspension was sequentially treated with *N*-methylaniline (306 µl, 3.0 mmol), 2-bromonaphthalene (621 mg, 3.0 mmol) and, after an additional 30 min, a suspension of Pd $(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4b** (28 mg, 0.06 mmol) in diglyme (2 mL). After being stirred at 120 °C for 1 d, the reaction mixture was passed through silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane) to give 547 mg (78%) of compound **38** as a yellow-orange oil. IR (neat): υ = 3056, 2876, 2811, 1712, 1627, 1592, 1493, 1388, 1365, 1321, 1228, 1192, 1135, 1120, 1086, 1060, 1025, 951, 836, 748, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.33 (s, 3H), 6.92 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 2.2 Hz, *J* = 9.0 Hz, 1H), 7.23 (m, 4H), 7.32 (m, 1H), 7.61 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 40.68 (q, 1C), 114.65 (d, 1C), 121.44 (d, 1C), 121.83 (d, 1C), 122.04 (d, 1C), 122.04 (d, 1C), 123.78 (d, 1C), 126.31 (d, 1C), 126.78 (d, 1C), 127.58 (d, 1C), 128.62 (d, 1C), 129.18 (s, 1C), 129.34 (d, 2C), 134.71 (s, 1C), 146.60 (s, 1C), 149.08 (s, 1C). MS (EI$^+$, 70 eV): *m/z* = 233 (1 0 0) [M$^+$], 217 (35). HRMS (EI$^+$, 70 eV): *m/z* = $C_{17}H_{15}N$ calcd. 233.1204; found 233.1196.

### 4.13. 4-Naphthalen-2-yl-morpholine (39)

NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (8 mL) was added and after 30 min, the resulting suspension was sequentially treated with morpholine (288 µl, 3.0 mmol), 2-bromonaphthalene (621 mg, 3.0 mmol) and,after stirring for an additional 30 min, a suspension of $Pd(OAc)_2$ (14 mg, 0.06 mmol) and ligand **4b** (28 mg, 0.06 mmol) in diglyme (3 mL). After being stirred at 120 °C for 1 d, the reaction mixture was passed through a bed of silica gel and the residue was washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 20:1) to give 482 mg (75%) of compound **39** as colourless solid, mp. 75 °C (hexane/acetone), mp.[46] 90 °C (ethanol). IR (neat): υ = 3051, 2961, 1893, 1712, 1628, 1598, 1446, 1364, 1266, 1255, 1220, 1122, 1067, 931, 878, 836, 807, 747 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.19 (t, *J* = 4.6 Hz, 4H), 3.84 (t, *J* = 4.6 Hz, 4H), 7.04 (s, 1H), 7.20 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.64 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 49.84 (t, 2C), 66.97 (t, 2C), 110.12 (d, 1C), 118.93 (d, 1C), 123.58 (d, 1C), 126.38 (d, 1C), 126.79 (d, 1C), 127.47 (d, 1C), 128.70 (s, 1C), 128.86 (d, 1C), 134.56 (s, 1C), 149.12 (s, 1C). MS (EI$^+$, 70 eV): *m/z* = 213 (88) [M$^+$], 155 (1 0 0), 127 (46). HRMS (EI$^+$, 70 eV): *m/z* = $C_{14}H_{15}NO$ calcd. 213.1154; found 213.1155.

Alternative procedure: NaO*t*Bu (577 mg, 6.0 mmol) was added to a dry round-bottom flask and the solid stirred for 12 h at 120 °C under Ar. Diglyme (8 mL) was added and after 60 min, the resulting suspension was sequentially treated with morpholine (288 µl, 3.0 mmol), 2-bromonaphthalene (621 mg, 3.0 mmol) and, after an additional 30 min, a suspension of $Pd(OAc)_2$ (14 mg, 0.06 mmol) and ligand **3** (27 mg, 0.06 mmol) in diglyme (3 mL). After being stirred at 120 °C for 2 d, the reaction mixture was passed through silica gel and the residue was

washed with MeOH. The filtrate was evaporated to dryness in vacuo and the residue was subjected to flash column chromatography on silica gel (hexane/acetone, 20:1) to give 355 mg (56%) of compound **39** as colourless solid, mp. 75 °C (hexane/acetone).

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## References

1. Hartwig JF. *Synlett.* 1997:329–340.
2. a) Demchuk OM, Yoruk B, Blackburn T, Snieckus V. *Synlett.* 2006:2908–2913;

   b) for reviews on the DoM-cross coupling strategy, see Snieckus V, Anctil EJ-G. de Meijere A, Braese S, Oestreich M, eds. *Metal-Catalyzed Cross-Coupling Reactions and More.* Vol. 3. 2014; 2014:1067–1133;

   c) Board J, Cosman J, Rantanen T, Singh S, Snieckus V. *Platinum. Metals Rev.* 2013;57:234–258.
3. Brenstrum T, Clattenburg J, Britten J, et al. *Org Lett.* 2006;8:103–105.
4. Ding H, Kang J, Hanson BE, Kohlpaintner CW. *J Mol Cat A Chem.* 1997;124:21–28.
5. Tomori H, Fox JM, Buchwald SL. *J Org Chem.* 2000;65:5334–5341.
6. Wagaw S, Buchwald SL. *J Org Chem.* 1996;61:7240–7241.
7. Louise J, Hartwig JF. *J Org Chem.* 1997;119:11,695–11,696.
8. Wolfe JP, Buchwald SL. *J Org Chem.* 1997;62:6066–6068.
9. Harris MC, Geis O, Buchwald SL. *J Org Chem.* 1999;64:6019–6022.
10. Wolfe JP, Buchwald SL. *J Org Chem.* 2000;65:1144–1157.
11. Mann G, Hartwig JF, Driver MS, Fernández-Rivas C. *J Am Chem Soc.* 1998;120:827–828.
12. Marcoux J-F, Wagaw S, Buchwald SL. *J Org Chem.* 1997;62:1568–1569.
13. Kataoka N, Shelby Q, Stambuli JP, Hartwig JF. *J Org Chem.* 2002;67:5553–5566.
14. Shen Q, Shekhar S, Stambuli JP, Hartwig JF. *Angew Chem Int Ed.* 2005;44:1371–1375.
15. Mul WP, Ramkisoensing K, Kamer PCJ, et al. *Adv Synth Catal.* 2002;344:293–298.
16. Yin J, Buchwald SL. *J Am Chem Soc.* 2002;124:6043–6048.
17. Kranenburg M, van der Burgt YEM, Kamer PCJ, van Leeuwen PWNM. *Organometallics.* 1995;14:3081–3089.
18. Guari Y, van Es DS, Reek JNH, Kamer PCJ, van Leeuwen PWNM. *Tetrahedron Lett.* 1999;40:3789–3790.
19. Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. *J Org Chem.* 2000;65:1158–1174.
20. Strieter ES, Blackmond DG, Buchwald SL. *J Am Chem Soc.* 2003;125:13,978–13,980.
21. Marion N, Ecarnot EC, Navarro O, Amoroso D, Bell A, Nolan SP. *J Org Chem.* 2006;71:3816–3821.
22. Huang J, Grasa G, Nolan SP. *Org Lett.* 1999;1:1307–1309.
23. Kunz EG. *Fr Pat.* 1975;2314:910.
24. Hermann WA, Kohlpaintner CW, Mantsberger RB, Bahrmann H, Kottmann H. *J Mol Cat A Chem.* 1995;97:65–72.
25. Gulyás H, Szöllösy Á, Szabó P, Halmos P, Bakos J. *Eur J Org Chem.* 2003:2775–2781.
26. Genin E, Amengual R, Michelet V, et al. *Adv Synth Catal.* 2004;346:1733–1741.
27. Kamer PCJ, Reek JNH, Van Leeuwen PWNM. in: Cornils, B. Herrmann WA, (eds.), Aqueous-phase organometallic catalysis (2nd Ed.). Wiley-VCH, Weinheim; 2004: p. 686–698.
28. Schreuder Goetheijt M, Kamer PCJ, van Leeuwen PWNM. *J Mol Cat A Chem.* 1998;134:243–249.
29. Buchwald SL, Mauger C, Mignani G, Scholz U. *Adv Synth Catal.* 2006;348:23–39.
30. Hartwig JF, Kawatsura M, Hauck SI, Shaughnessy KH, Alcazar-Roman LM. *J Org Chem.* 1999;64:5575–5580.
31. Hamann BC, Hartwig JF. *J Am Chem Soc.* 1998;120:7369–7370.
32. Paradies J. Metal-catalyzed cross-coupling reactions and more. In: de Miejere A, Braese S, Oestereich M, eds. Weinheim: Wiley-VCH; 2014 p. 995.
33. Charles MD, Schultz P, Buchwald SL. *Org Lett.* 2005;7:3965–3968.
34. Lee S, Jørgensen M, Hartwig JF. *Org Lett.* 2001;3:2729–2732.
35. Kiritsy JA, Yung DK. *J Med Chem.* 1978:1301–1307.
36. D'Aproano G, Schiavon G, Zotti G, Leclerc M. *Chem Mater.* 1995;7:33–42.
37. Sakamoul K, Motoda M, Sugimoto M, Sakaki S. *J Phys Chem A.* 1999;103:5551.
38. Begouin A, Hesse S, Queiroz M-JRP, Kirsch G. *Synthesis.* 2006:2794–2798.
39. Parrish CA, Buchwald SL. *J Org Chem.* 2001;66:3820–3827.
40. Meudt A, Nerdinger S, Lehnemann B, Jung J, Vogel T, Snieckus V. DE 102005030400.
41. Meudt A, Nerdinger S, Lehnemann B, Jung J, Vogel T, Snieckus V, WO 2007000250.
42. Anderson KW, Buchwald SL, Angew. Chem. Int. Ed. ; 2005, 44, p. 6173–6177; Buchwald SL, Anderson KW, WO2006/074315 A2.
43.. Bruker AXS Crystal Structure Analysis Package: Bruker (2000). SHELXTL. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA. Bruker (2005). XPREP. Version 2005/2. Bruker AXS Inc., Madison, Wisconsin, USA. Bruker (2005). SAINT. Version 7.23A. Bruker AXS Inc., Madison, Wisconsin, USA. Bruker (2006). APEX2. Version 2.0-2. Bruker AXS Inc., Madison, Wisconsin, USA.
44. Cromer DT, Waber JT, International Tables for X-ray Crystallography; Kynoch Press: Birmingham, UK, 1974; vol. 4, Table 2.2 A.
45. Ng Ph, Buu-Hoï. *J Chem Soc.* 1949:670–676.
46. Cretcher LH, Pittinger WH. *J Am Chem Soc.* 1925;47:163–166.