[2.2]Paracyclophane-based monophosphine ligand for palladium-catalyzed cross-coupling reactions of aryl chlorides†

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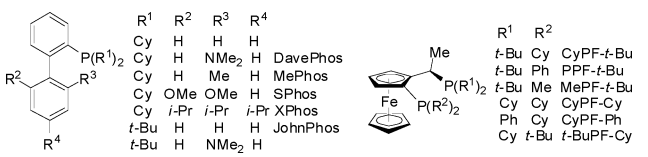
A new [2.2]paracyclophane-based electron-rich and sterically bulky monophosphine ligand has been synthesized by an efficient and straightforward method. When combined with palladium, this ligand shows excellent performance in the Buchwald–Hartwig amination and Suzuki–Miyaura coupling reactions of various aryl chlorides. In both types of reactions, *ortho*-substituted, deactivated aryl chlorides are shown to be viable substrates. However, the Suzuki–Miyaura coupling appears to be easier, with palladium loading at 0.1 mol% being feasible.

Introduction

Pd-catalyzed cross-coupling reactions have become powerful tools for the formation of new carbon–carbon and carbon–heteroatom bonds.[1] Among these reliable catalytic transformations, the Suzuki–Miyaura coupling[2] and Buchwald–Hartwig amination[2b,3] have received special attention and have been widely used in organic synthesis. Recently, research on these two reactions has focused on the use of readily available and comparatively cheap aryl chlorides as coupling partners, due to their particular relevance to industrial applications.[4] However, the high C–Cl bond strength renders their oxidative addition to palladium difficult, thus often necessitating high catalyst loadings and so increasing the cost in catalysts.[5] It has been well recognized that ligands employed for palladium significantly impact on the outcome of the reactions, with a number of reports showing that Pd complexes derived from sterically hindered and electron-rich phosphines are effective catalysts,[6,7] *e.g.* PCy_3, $P(t\text{-Bu})_3$, SPhos, CyPF-*t*-Bu, and their analogues (Scheme 1). However, there is still significant room for improvement in the catalyst performance. And in particular, developing simple and readily accessible ligands with comparable, if not better, ability at assisting the metal-catalyzed coupling reactions is still necessary.



Scheme 1 Representative ligands used for Buchwald–Hartwig amination and Suzuki–Miyaura coupling reactions of aryl chlorides.

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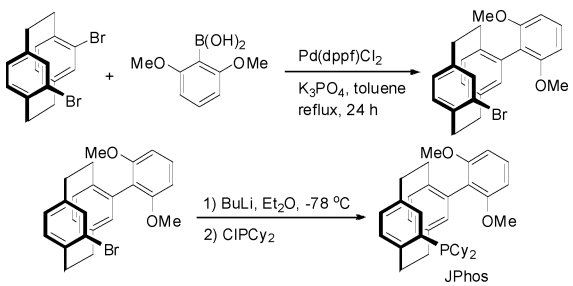
Due to its unique skeleton, [2.2]paracyclophane possesses unique electronic and steric properties.[8] Not surprisingly, ligands derived from it have been applied to various catalytic reactions, especially those in asymmetric synthesis.[8] Herein we report the first synthesis of an electron-rich and sterically bulky monophosphine ligand based on [2.2]paracyclophane and its application in the Suzuki–Miyaura coupling and Buchwald–Hartwig amination of aryl chlorides. In related work, we showed that these reactions can also be effected with ferrocenyl monophosphine ligands.[9,10]

Results and discussion

The ligand was synthesised *via* an easy, two-step process. As shown in Scheme 2, using the commercially available racemic 4,12-dibromo[2.2]paracyclophane as the starting material, the aryl-substituted 4-bromo[2.2]paracyclophane intermediate was readily obtained by the Suzuki–Miyaura coupling with 2,6-dimethoxyphenylboronic acid catalyzed by $Pd(dppf)Cl_2$.[11] After lithiation of the intermediate and then treating with chlorodicyclohexylphosphine, the desired bulky and electron-rich monophosphine ligand, JPhos, was afforded in 56% overall yield.



Scheme 2 Synthesis of (*rac*)-[2.2]paracyclophane-based JPhos.

We were unable to grow single crystals of the free ligand and so could not discern the steric environment around the phosphorus. Fortunately, we obtained suitable crystals of its oxide and were able to determine its X-ray structure. As can be seen from Fig. 1, the 2,6-dimethoxyphenyl and one of the cyclohexyl groups are nearly perpendicular to the benzene rings of the

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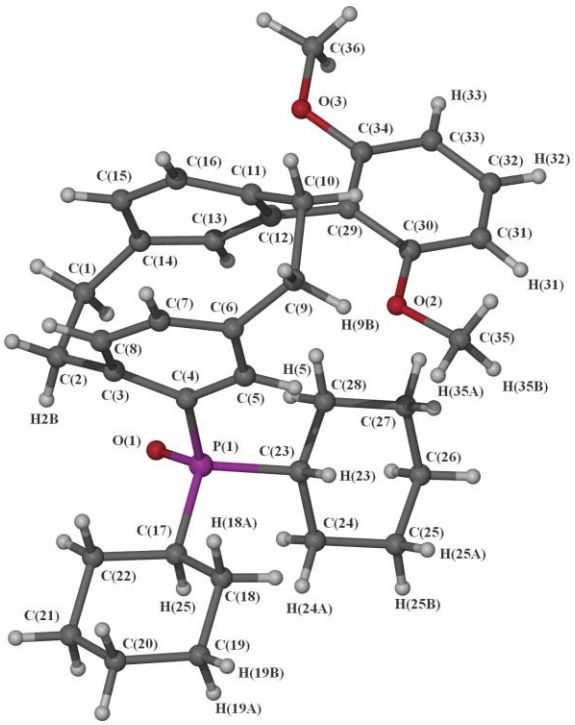


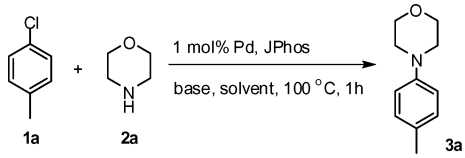
Fig. 1 X-Ray crystal structure of JPhos oxide. Selected distances [Å] and torsion angles [°]: C(1)-C(2) 1.584(2), C(2)-C(3) 1.515(2), C(1)-C(14) 1.513(2), C(6)-C(9) 1.513(2), C(9)-C(10) 1.599(2), C(10)-C(11) 1.511(2), O(1)-P(1)-C(4)-C(3) 38.3, O(1)-P(1)-C(4)-C(5) −143.5, C(30)-C(29)-C(12)-C(13) −113.9, C(30)-C(29)-C(12)-C(11) 70.3, C(17)-P(1)-C(4)-C(5) 95.3.

[2.2]paracyclophane, with the other cyclohexyl group pointing towards the 2,6-dimethoxyphenyl ring and the oxygen atom in the dicyclohexylphosphine oxide towards one of the ethylene bridges. Thus, replacing the oxygen with palladium would place the latter in a sterically demanding environment, with half of the space being likely blocked by the auxiliary groups on the phosphorus.

The [2.2]paracyclophane backbone is strained. The distance between the carbon atoms C3, C14 and C6, C11 across the cyclophane system (2.783 and 2.784 Å) is less than twice the van der Waals radius of a C atom. There are also short contacts between atoms of the paracyclophane and the adjacent methoxy groups (*e.g.* O3···C12 2.683 Å, H9B···H35A 2.360 Å), the phosphine oxide (*e.g.* O1···H2B 2.468 Å) and the cyclohexyl groups (*e.g.* H5···H23 2.231 Å), leading to a sterically hindered system. The distortion is also borne out by the unusually large torsion angles for the benzene rings, even for paracyclophane systems (−18° for the bonded atoms C16-C11-C12-C13).[12] The conformation of both benzene rings is boat, with ring puckering parameter S = 0.22 Å, 0.20 Å.[13]

With the ligand in hand, we set out to examine its potential use in the Buchwald–Hartwig amination. The reaction between 4-chlorotoluene (**1a**) and morpholine (**2a**) was first examined (Table 1). After screening various conditions, we found that $Pd_2(dba)_3$ was more efficient than $Pd(OAc)_2$, and the best result was furnished when the ratio of JPhos/Pd was set to 2 (entry 4). Whilst the solvent did not appear to affect the reaction significantly, dioxane gave a better yield (*e.g.* entries 4 *vs* 7). In contrast, base plays an important role, with better

Table 1 Optimization of reaction conditions for the Buchwald–Hartwig amination[a]



Entry	Pd	Pd/ligand (mol/mol)	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	1/2	K_3PO_4	dioxane	8
2	$Pd_2(dba)_3$	1/2	K_3PO_4	dioxane	12
3	$Pd(OAc)_2$	1/2	NaO^{t}Bu	dioxane	40
4	$Pd_2(dba)_3$	1/2	NaO^{t}Bu	dioxane	80
5	$Pd_2(dba)_3$	1/1	NaO^{t}Bu	dioxane	65
6	$Pd_2(dba)_3$	1/3	NaO^{t}Bu	dioxane	20
7	$Pd_2(dba)_3$	1/2	NaO^{t}Bu	toluene	70
8	$Pd_2(dba)_3$	no ligand	NaO^{t}Bu	dioxane	0

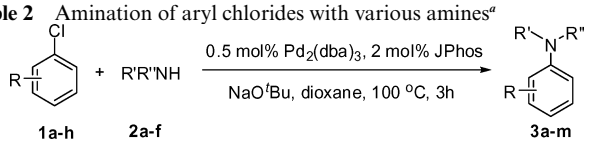
[a] Reactions were carried out with **1a** (1.0 mmol), **2a** (1.2 equiv), base (1.4 equiv), palladium catalyst (1 mol%), and JPhos in 4 mL solvent at 100 °C for 1 h. [b] Isolated yields.

results obtained when using a strong one, such as NaO^{t}Bu (entries 2 *vs* 4). A control experiment without ligand was also performed, affording no desired product (entry 8), and thus suggesting that the active catalytic species are palladium-ligand complexes.

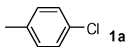
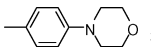
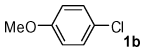
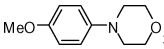
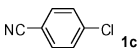
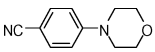
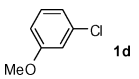
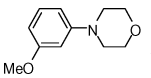
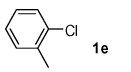
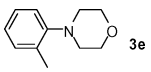
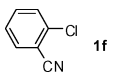
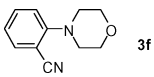
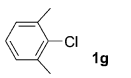
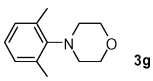
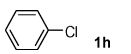
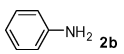
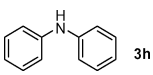
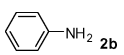
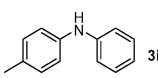
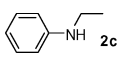
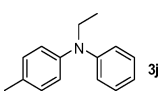
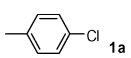
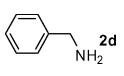
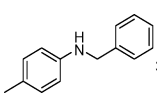
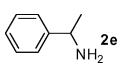
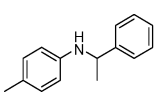
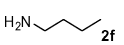
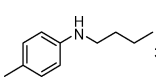
Having established the optimized conditions, we then studied the amination of a series of aryl chlorides (**1a–h**) with various amines (**2a–f**). The results are shown in Table 2. As can be seen, in most cases, the reactions afforded good to excellent yields of the corresponding aniline products **3a–m** under a low catalyst loading (0.5 mol% $Pd_2(dba)_3$). In the case of the amination with morpholine (**2a**), it appears that aryl chlorides with electron-withdrawing groups tend to furnish lower yields (entries 3 and 6). *ortho* Substituents on the aryl rings are tolerated; but the corresponding products were obtained in lower yields (entries 5–7). In particular, only a 60% yield was obtained in 6 h when 2,6-dimethyl-chlorobenzene (**1g**) was used (entry 7). This Pd-JPhos catalyst also worked well with aniline derivatives; examples are seen in entries 8–10. We further examined the amination of 4-chlorotoluene (**1a**) with several primary aliphatic amines, again obtaining good results (entries 11–13).

The high activity of the catalyst in the amination reactions prompted us to explore its applications in the Suzuki–Miyaura coupling of aryl chlorides. Using commonly adopted conditions in the literature,[6,9] we first tested the reaction between 4-chlorobenzene (**1h**) and phenylboronic acid (**4a**). An excellent result (93% yield) was obtained when the reaction was catalyzed with only 0.1 mol% $Pd(OAc)_2$ and 0.2 mol% JPhos in dioxane at 80 °C for 12 h. As with the Buchwald–Hartwig amination, however, no desired product was afforded without the ligand. Having obtained this encouraging result, we then extended the chemistry into the coupling of a series of aryl chlorides (**1a–k**) with several aryl boronic acids (**4a–d**) under the same reaction conditions. The results are summarized in Table 3. High yields were achieved for all the examples, although some of the sterically bulkier substrates necessitated a higher catalyst loading (entries 10, 12 and 13). For the coupling reactions with phenylboronic

Table 2 Amination of aryl chlorides with various amines[a]

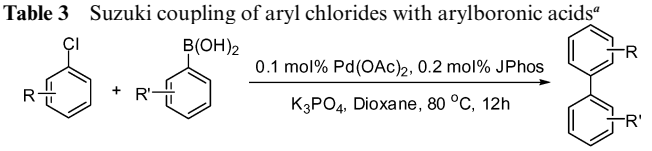


1a-h 2a-f 3a-m

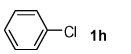
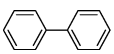
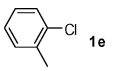
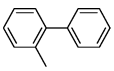
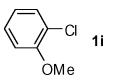
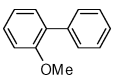
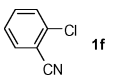
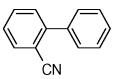
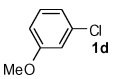
Entry	ArCl	Amine	Product	Yield[b] (%)
1	 1a		 3a	95
2	 1b		 3b	94
3	 1c		 3c	88
4	 1d	 2a	 3d	97
5	 1e		 3e	85
6	 1f		 3f	65
7[c]	 1g		 3g	60
8[c]	 1h	 2b	 3h	91
9[c]		 2b	 3i	89
10[c]		 2c	 3j	81
11	 1a	 2d	 3k	93
12		 2e	 3l	90
13[c]		 2f	 3m	93

[a] Reactions were carried out with **1** (1.0 mmol), **2** (1.2 equiv), NaO^{t}Bu (1.4 equiv), $Pd_2(dba)_3$ (0.5 mol%), and JPhos (2 mol%) in 4 mL dioxane at 100 °C for 3 h. [b] Isolated yields. [c] 6 h reaction time.

Table 3 Suzuki coupling of aryl chlorides with arylboronic acids[a]



1a-k 4a-d 5a-m

Entry	ArCl	$ArB(OH)_2$	Product	Yield[b] (%)
1	 1h		 5a	93
2	 1e		 5b	90
3	 1i		 5c	87
4	 1f		 5d	90
5	 1d	4a	5e	96
6	1a		5f	92
7	1b		5g	90
8	1c		5h	95
9	1j		5i	97
10[c]	1g		5j	86
11	1b	4b	5k	93
12[c]	1e	4c	5l	84
13[d]	1k	4d	5m	91

[a] Reactions were carried out with **1** (1.0 mmol), **4** (1.5 equiv), K_3PO_4 (3.0 equiv), $Pd(OAc)_2$ (0.1 mol%), and JPhos (0.2 mol%) in 4 mL dioxane at 80 °C for 12 h. [b] Isolated yields. [c] 0.2 mol% $Pd(OAc)_2$ and 0.4 mol% JPhos used. [d] 0.6 mol% $Pd(OAc)_2$ and 1.2 mol% JPhos used.

acid (**4a**), *ortho* substituted aryl chlorides afforded hindered biaryl products in slightly lower yields (entries 2–4), so did the more electron-rich aryl chlorides (entries 2, 3, 6 and 7). Of further note is that an excellent yield was obtained for the substituted bromonaphthalene substrate (entry 13), demonstrating the potential of a chiral version of JPhos in the synthesis of chiral binaphthalene compounds.

Conclusion

In summary, we have developed an electron-rich and sterically bulky monophosphine ligand *via* a simple synthetic pathway. With a palladium catalyst derived from JPhos, the Buchwald–Hartwig amination and Suzuki–Miyaura coupling reactions of various aryl chlorides, including some unactivated and hindered ones, can be

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readily performed. The [2.2]paracyclophane backbone is seen to bestow modularity and easy accessibility on ligands of this type. Further work on the ligands and their application in asymmetric catalysis are underway.

Experimental

General

All the reactions were carried out under a nitrogen atmosphere with dried solvents unless otherwise indicated. (*rac*)-4,12-Dibromo[2.2]paracyclophane was provided by Johnson Matthey. The following chemicals were purchased from Lancaster or Aldrich and used as received: all the aryl chlorides, arylboronic acids, amines, $Pd(dppf)Cl_2$, $Pd(dba)_2$, $Pd(OAc)_2$, *n*-BuLi, chlorodicyclohexylphosphine ($ClPCy_2$), $NaOBu^t$, and K_3PO_4. Silica gel plates (GF_{254}) were used for TLC and silica gel (230–400 mesh) was used for flash column chromatography. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI).

Preparation of (*rac*)-4-bromo-12-(2′,6′-dimethoxy)phenyl-[2.2]paracyclophane[11]. An oven-dried Schlenk tube containing a stir bar was charged with (*rac*)-4,12-dibromo[2.2]paracyclophane (1.83 g, 5.0 mmol), 2,6-dimethoxyphenylboronic acid (1.37 g, 7.5 mmol, 1.5 equiv), $Pd(dppf)Cl_2$ (164 mg, 0.20 mmol, 4 mol%), and K_3PO_4 (2.12 g, 10.0 mmol, 2.0 equiv). After degassing three times with nitrogen, freshly distilled toluene (20 mL) was injected. The reaction mixture was vigorously stirred at 115 °C for 24 h. After cooling down to room temperature, 30 mL toluene was added, and the mixture was hydrolyzed with 10% NaOH (30 mL). This was followed by phase separation and extraction of the aqueous phase with EtOAc (3 × 25 mL). The collected organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (25/75) as eluant to afford a white solid product (1.82 g, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, $J = 8.4$ Hz, 1H), 7.10 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 6.73 (s, 1H), 6.67 (s, 2H), 6.54–6.51 (m, 2H), 6.39 (d, $J = 7.6$ Hz, 1H), 4.10 (s, 3H), 3.60–3.51 (m, 1H), 3.48 (s, 3H), 3.22–3.10 (m, 2H), 2.95–2.75 (m, 4H), 2.65–2.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.5, 141.6, 140.8, 139.7, 137.4, 137.1, 134.6, 133.5, 133.0, 131.6, 131.3, 129.8, 129.0, 126.9, 118.5, 105.1, 105.0, 56.5, 55.8, 37.3, 34.9, 34.8, 32.9; MS (CI, *m/z*, %) 442:440 = 1:1 (100) $[M+H+NH_3]^+$, 425:423 = 1:1 (72) $[M+H]^+$.

Synthesis of (*rac*)-4-dicyclohexylphosphino-12-(2′,6′-dimethoxy)phenyl-[2.2]paracyclophane (JPhos). An oven-dried Schlenk flask was charged with 4-bromo-12-(2′,6′-dimethoxy)phenyl-paracyclophane (1.06 g, 2.5 mmol). After degassing three times with nitrogen, 50 mL freshly distilled Et_2O was introduced. After cooling to −78 °C, 1.3 mL (3.3 mmol, 2.5 M in hexane) *n*-BuLi was dropwise added. The solution was stirred at −78 °C for 2 h, and for another 3 h after being gradually warmed to room temperature. $ClPCy_2$ (0.66 mL, 3.0 mmol) was then added, and the mixture was stirred at room temperature overnight. Thereafter, 0.5 mL 1 M NaOH was introduced and after stirring for 10 min, the solvent was removed. The crude product was purified by flash column chromatography (hexane) on silica gel, affording a white solid product (0.89 g, 66% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, $J = 8.4$ Hz, 1H), 6.77–6.66 (m, 4H), 6.51–6.46 (m, 3H), 6.43 (s, 1H), 4.08 (s, 3H), 4.06–4.01 (m, 1H), 3.39 (s, 3H), 3.25–2.88 (m, 6H), 2.85–2.77 (m, 1H), 2.08–2.00 (m, 1H), 1.98–1.85 (m, 1H), 1.84–1.55 (m, 6H), 1.46–1.37 (m, 3H), 1.30–0.73 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.7, 146.6 (d, $J = 23.3$ Hz), 138.3, 138.2, 137.4, 135.0–134.4 (m), 133.8, 133.4, 133.3, 130.7, 128.4, 118.5, 105.2, 104.0, 56.5, 55.2, 37.1 (d, $J = 16.0$ Hz), 35.0–34.7 (m), 34.2, 31.9 (d, $J = 21.8$ Hz), 30.8 (d, $J = 16.0$ Hz), 29.1 (d, $J = 10.9$ Hz), 28.7 (d, $J = 10.2$ Hz), 28.1 (d, $J = 13.8$ Hz), 27.7–27.5 (m), 27.2 (d, $J = 14.6$ Hz), 26.7 (d, $J = 22.6$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.72; MS (CI, *m/z*, %) 541 (100) $[M+H]^+$; Anal. calcd for $C_{36}H_{45}O_2P$: C, 79.97; H, 8.39. Found: C, 79.97; H, 8.44.

X-Ray structural determination

Crystals of (*rac*)-dicyclohexyl-[12-(2′,6′-dimethoxy)phenyl-[2.2]-paracyclophan-4-yl]-phosphine oxide (JPhos oxide) were grown in a mixture of hexane and ethyl acetate (1:1) at room temperature.

Crystal data. $C_{36}H_{45}O_3P$, $M = 556.69$, colourless block, 0.37 × 0.31 × 0.28 mm^3, monoclinic, space group $P2_1/n$ (No. 14), $a = 9.4191(11)$, $b = 20.304(3)$, $c = 15.4161(18)$ Å, $\beta = 97.671(2)°$, $V = 2921.9(6)$ $Å^3$, $Z = 4$, $D_c = 1.265$ g/cm^3, $F_{000} = 1200$, Bruker D8 diffractometer with APEX detector, MoKα radiation, $\lambda = 0.71073$ Å, $T = 110(2)$ K, $2\theta_{max} = 55.0°$, 16429 reflections collected, 6447 unique ($R_{int} = 0.0272$). Final $GoF = 1.019$, $R1 = 0.0441$, $wR2 = 0.1008$, R indices based on 5107 reflections with I >2sigma(I) (refinement on F^2), 520 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.130$ mm^{-1}.

General procedure for the Buchwald–Hartwig amination of aryl chlorides

An oven-dried carousel reaction tube containing a stir bar was charged with $Pd_2(dba)_3$ (0.005 mmol, 0.5 mol%), JPhos (0.02 mmol, 2 mol%), and NaO*t*Bu (1.4 mmol). After degassing three times with nitrogen, freshly distilled dioxane (4 mL), an aryl chloride **1a-h** (1 mmol), and an amine **2a-f** (1.2 mmol) were injected sequentially. The reaction mixture was vigorously stirred at 100 °C for the time mentioned in Table 2. After cooling to room temperature, 15 mL EtOAc was added and the mixture was washed with 5 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on basic Al_2O_3 using a mixture of ethyl acetate and hexane (10/90 to 50/50) as eluant. The desired products **3a–m** were obtained in 60–97% yields (Table 2).

***N*-(4-Methylphenyl)morpholine (3a)[16].** ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, $J = 8.4$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 3.78 (t, $J = 4.8$ Hz, 4H), 3.02 (t, $J = 4.8$ Hz, 4H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 130.1, 129.9, 116.5, 67.4, 50.4, 20.8; MS (CI, *m/z*,%) 178 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.67; H, 8.63; N, 7.83.

***N*-(4-Methoxyphenyl)morpholine (3b)[16].** ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–6.83 (m, 4H), 3.85 (t, $J = 4.8$ Hz, 4H), 3.76 (s, 3H), 3.05 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5,

146.1, 118.2, 114.9, 67.4, 56.0, 51.3; MS (CI, *m/z*,%) 194 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.33; H, 7.86; N, 7.18.

***N*-(4-Cyanophenyl)morpholine (3c)[16].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 3.84 (t, J = 4.8 Hz, 4H), 3.28 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 133.9, 120.2, 114.5, 101.3, 66.8, 47.7; MS (CI, *m/z*,%) 189 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.10; H, 6.42; N, 14.85.

***N*-(3-Methoxyphenyl)morpholine (3d)[16].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.45–6.41 (m, 2H), 3.81 (t, J = 4.8 Hz, 4H), 3.76 (s, 3H), 3.12 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 153.2, 130.3, 108.9, 105.2, 102.7, 67.3, 55.6, 49.7; MS (CI, *m/z*, %) 194 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.44; H, 7.88; N, 7.19.

***N*-(2-Methylphenyl)morpholine (3e)[14].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.14 (m, 2H), 7.02–6.98 (m, 2H), 3.83 (t, J = 4.8 Hz, 4H), 2.89 (t, J = 4.8 Hz, 4H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 133.1, 131.6, 127.1, 123.9, 119.4, 67.9, 52.7, 18.3; MS (CI, *m/z*, %) 178 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.47; H, 8.55; N, 7.87.

***N*-(2-Cyanophenyl)morpholine (3f)[15].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.06–7.00 (m, 2H), 3.90 (t, J = 4.8 Hz, 4H), 3.21 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 132.6, 132.0, 120.3, 116.7, 116.4, 104.4, 65.1, 50.0; MS (CI, *m/z*, %) 189 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.40; H, 6.50; N, 14.70.

***N*-(2,6-Dimethylphenyl)morpholine (3g)[17].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.86 (m, 3H), 3.80 (t, J = 4.8 Hz, 4H), 3.10 (t, J = 4.8 Hz, 4H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 135.4, 127.5, 123.8, 66.6, 48.4, 17.9; MS (CI, *m/z*,%) 192 (100) $[M+H]^+$; Anal. calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.47; H, 8.84; N, 7.36.

Diphenylamine (3h)[16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 4H), 7.06 (d, J = 8.8 Hz, 4H), 6.92 (t, J = 7.6 Hz, 2H), 5.68 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 129.7, 121.4, 118.3; MS (CI, *m/z*,%) 170 (100) $[M+H]^+$; Anal. calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.32; H, 6.58; N, 8.26.

4-Methyl-*N*-phenylaniline (3i)[7h]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.20 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.02–6.98 (m, 4H), 6.90–6.85 (m, 1H), 5.59 (br, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 140.8, 131.4, 130.3, 129.7, 120.7, 119.4, 117.3, 21.0; MS (CI, *m/z*,%) 184 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.12; H, 7.23; N, 7.70.

***N*-Ethyl-4-methyl-*N*-phenylaniline (3j)[7h].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.17 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.89–6.82 (m, 3H), 3.73 (q, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 145.5, 132.5, 130.4, 129.5, 123.9, 119.8, 118.7, 46.8, 21.1, 13.1; MS (CI, *m/z*,%) 212 (100) $[M+H]^+$; Anal. calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.10; H, 8.06; N, 6.67.

***N*-Benzyl-4-methylaniline (3k)[16].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H), 7.28–7.24 (m, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 2H), 4.30 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 140.1, 130.2, 129.0, 127.9, 127.6, 127.2, 113.5, 49.1, 20.8; MS (CI, *m/z*,%) 198 (100) $[M+H]^+$; Anal. calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.10; H, 7.61; N, 7.14.

4-Methyl-*N*-(1-phenylethyl)aniline (3l)[18]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 4H), 7.24–7.18 (m, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.44 (d, J = 8.0 Hz, 2H), 4.44 (q, J = 6.8 Hz, 1H), 3.95 (br, 1H), 2.18 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 145.4, 130.0, 129.0, 127.2, 126.8, 126.3, 113.9, 54.1, 25.4, 20.7; MS (CI, *m/z*,%) 212 (100) $[M+H]^+$; Anal. calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.60; H, 8.13; N, 6.56.

***N*-Butyl-4-methylaniline (3m)[7h].** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 3.35 (br, 1H), 3.08 (t, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.61–1.55 (m, 2H), 1.45–1.40 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 130.1, 126.7, 113.3, 44.5, 32.2, 20.8, 20.7, 14.3; MS (CI, *m/z*,%) 164 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.85; H, 10.64; N, 8.54.

General procedure for the Suzuki–Miyaura reaction of aryl chlorides

An oven-dried carousel reaction tube containing a stir bar was charged with a boronic acid **4a-d** (1.5 mmol), K_3PO_4 (3 mmol), and JPhos (0.002 mmol, 0.2 mol%). After degassing three times with nitrogen, an aryl chloride **1a-k** (1 mmol), 0.5 mL $Pd(OAc)_2$ solution (2×10^{-3} M in dioxane, 0.001 mmol, 0.1 mol%), and freshly distilled dioxane (4 mL) were injected sequentially. The reaction mixture was vigorously stirred at 80 °C for 12 h. After cooling to room temperature, 15 mL EtOAc was added and the mixture was washed with 5 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (5/95 to 20/80) as eluant. The desired products **5a-m** were obtained in 84–97% yields (Table 3).

Biphenyl (5a)[16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 4H), 7.46–7.40 (m, 4H), 7.36–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 129.3, 127.7; MS (CI, *m/z*,%) 155 (100) $[M+H]^+$; Anal. calcd for $C_{12}H_{10}$: C, 93.46; H, 6.54. Found: C, 93.45; H, 6.50.

2-Methylbiphenyl (5b)[16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.33–7.29 (m, 3H), 7.26–7.21 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.9, 135.4, 130.3, 129.8, 129.2, 128.1, 127.3, 126.8, 125.8, 20.4; MS (CI, *m/z*,%) 168 (100) $[M]^+$; Anal. calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.75; H, 7.27.

2-Methoxybiphenyl (5c)[19]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2H), 7.42–7.37 (m, 2H), 7.33–7.28 (m, 3H), 7.02–6.96 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 139.0, 131.3, 131.2, 130.0, 129.0, 128.4, 127.3, 121.3, 111.7, 56.0; MS (CI, *m/z*,%) 185 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.82; H, 6.64.

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Biphenyl-2-carbonitrile (5d)[7h]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.53–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 138.6, 134.1, 133.2, 130.5, 129.2, 129.1, 127.9, 119.1, 111.8; MS (CI, *m*/*z*,%) 180 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.20; H, 5.00; N, 7.80.

3-Methoxybiphenyl (5e)[20]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.37–7.32 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.12 (s, 1H), 6.90 (d, J = 7.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 143.2, 141.6, 130.1, 129.1, 127.8, 127.6, 120.1, 113.4, 113.1, 55.7; MS (CI, *m*/*z*, %) 185 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.70; H, 6.67.

4-Methylbiphenyl (5f)[7h]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.35–7.29 (m, 1H), 7.24 (d, J = 7.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.8, 137.4, 129.9, 129.2, 129.1, 127.5, 127.4, 21.5; MS (CI, *m*/*z*,%) 168 (100) $[M]^+$; Anal. calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.71; H, 7.17.

4-Methoxybiphenyl (5g)[15]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.50 (m, 4H), 7.43–7.38 (m, 2H), 7.32–7.28 (m, 1H), 6.97 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 141.3, 134.2, 129.1, 128.6, 127.1, 127.0, 114.6, 55.7; MS (CI, *m*/*z*,%) 185 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.80; H, 6.57.

Biphenyl-4-carbonitrile (5h)[21]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.51–7.46 (m, 2H), 7.42 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.6, 133.0, 129.5, 129.1, 128.1, 127.6, 119.3, 111.4; MS (CI, *m*/*z*,%) 180 (100) $[M+H]^+$; Anal. calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.05; H, 5.01; N, 7.94.

4-Acetylbiphenyl (5i)[22]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.49–7.44 (m, 2H), 7.42–7.37 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 146.2, 140.3, 136.3, 129.4, 129.3, 128.6, 127.7, 127.6, 27.0; MS (CI, *m*/*z*,%) 197 (100) $[M+H]^+$; Anal. calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.53; H, 6.14.

2,6-Dimethylbiphenyl (5j)[22]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 7.6 Hz, 2H), 7.35–7.31 (m, 1H), 7.16–7.09 (m, 5H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 141.5, 136.4, 129.4, 128.8, 127.7, 127.4, 127.0, 21.2; MS (CI, *m*/*z*,%) 182 (100) $[M]^+$; Anal. calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.38; H, 7.68.

4,4′-Dimethoxybiphenyl (5k)[21]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.8 Hz, 4H), 6.95 (d, J = 8.8 Hz, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 133.9, 128.1, 114.6, 55.7; MS (CI, *m*/*z*,%) 215 (100) $[M+H]^+$; Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.37; H, 6.64.

2,2′-Dimethylbiphenyl (5l)[16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 6H), 7.09 (d, J = 7.2 Hz, 2H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 136.2, 130.2, 129.7, 127.6, 126.0, 20.2; MS (CI, *m*/*z*,%) 182 (100) $[M]^+$; Anal. calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.09; H, 7.78.

2-Methoxy-1,1′-binaphthyl (5m)[23]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 1H), 7.94–7.90 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.4, 6.8 Hz, 1H), 7.44–7.40 (m, 3H), 7.33–7.30 (m, 2H), 7.29–7.13 (m, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 135.0, 134.7, 134.2, 133.4, 129.9, 129.5, 128.9, 128.7, 128.2, 128.1, 126.8, 126.6, 126.3, 126.1, 126.0, 125.9, 124.0, 123.8, 114.4, 57.2; MS (CI, *m*/*z*,%) 285 (100) $[M+H]^+$; Anal. calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.77; H, 5.64.

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