An Improved Method for the Palladium-Catalyzed Amination of Aryl Iodides

Mayssam H. Ali and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

sbuchwal@mit.edu

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Aryl iodides are coupled with amines to give the corresponding arylamines in high yield in the presence of palladium, a suitable ligand, and NaO*t*-Bu. Functionalized aryl iodides give good yields of the corresponding arylamines when Cs_2CO_3 is substituted as the base.

Introduction

Arylamines are attractive targets for chemical synthesis because of their prevalence and wide utility. One of their earliest applications was in the production of brightly colored synthetic dyes, introduced in the late nineteenth century.[1] Arylamines have a large number of other applications and are thus attractive targets for chemical synthesis. They are found in biologically active compounds such as pharmaceuticals[2−4] and agrochemicals.[5] Several commonly occurring DNA lesions are arylamines, and they have been the target of recent synthetic efforts.[6−8] Arylamines have also been employed as ligands for transition metals,[9] and in the design of conductive polymers[10] and other electronically interesting materials.[11]

Traditional routes for the synthesis of these compounds such as electrophilic nitration and subsequent reduction, nucleophilic aromatic substitution, and Ullmann-type couplings often suffer from relatively harsh conditions and limited generality.[12,13] By contrast, the transition metal-mediated coupling of amines with aryl halides is regioselective, does not require activating groups, and occurs under relatively mild conditions. Since its discovery by Migita and co-workers in 1983,[14] and the initial breakthrough of a tin-free reaction,[15,16] this reaction has evolved into a general synthesis of substituted and unsubstituted anilines. There are a number of reviews highlighting recent progress in this area.[12,17−19] Much of this work has focused on the reactions of industrially relevant aryl chlorides and bromides.

It is also important to develop appropriate reaction conditions for aryl iodides, as they are widely used as substrates for palladium-catalyzed cross-coupling reactions. They are readily accessible intermediates for use in synthetic organic chemistry, e.g., by electrophilic iodination,[20] directed ortho metalation,[21] or by conversion of organometallic intermediates.[22] Moreover, a large selection is available from commercial sources. Although their cost is a deterrent on a production scale, they are invaluable both in academic and industrial laboratories.

Exceptional among palladium-catalyzed cross-coupling reactions, aryl iodides have historically been less effective substrates for the amination reaction than their bromide counterparts.[14,15,23] In the initial procedure developed in our group, it was found that aryl iodides were ineffective in the intermolecular amination reaction, whereas they outperformed aryl bromides in intramolecular aminations.[15]

The earliest work from these laboratories to focus on the intermolecular amination of aryl iodides employed P(*o*-tol)$_3$ and NaO*t*-Bu (the first generation improvement upon the Migita procedure).[24] The use of dioxane as solvent was critical to the success of this undertaking. Yields, on average, were lower than those of the corresponding aryl bromide substrates. After the discovery that chelating bisphosphines enhanced both substrate scope and reaction rates relative to the monodentate phosphine P(*o*-tol)$_3$,[25,26] it was found that a Pd/BINAP mixture, with NaO*t*-Bu as base, could catalyze the

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(2) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck Research Laboratories: Whitehouse Station, 1996.
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(5) *CRC Handbook of Pesticides*; Milne, G. W. A., Ed.; CRC Press: Boca Raton, 1994.
(6) Harwood, E. A.; Sigurdsson, S. T.; Edfeldt, N. B. F.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 5081−5082.
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(9) Greco, G. E.; Popa, A. I.; Schrock, R. R. *Organomet.* **1998**, *17*, 5591−5593.
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(11) Ito, A.; Taniguchi, A.; Yamabe, T.; Tanaka, K. *Org. Lett.* **1999**, *1*, 741−743.
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(13) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.
(14) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927−928.
(15) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350.
(16) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612.
(17) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(18) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.
(19) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067.
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(21) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.
(22) Frid, M.; Pérez, D.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9469−9470.
(23) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169−175.
(24) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135.

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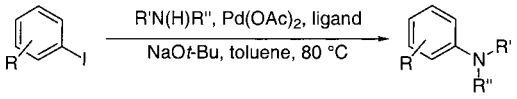
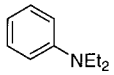
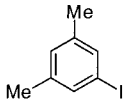
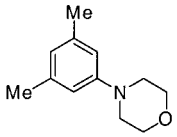
Table 1. Cyclohexyl and *tert*-Butyl Biphenyl Ligands for the Amination of Aryl Iodides

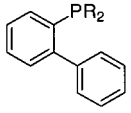


Entry	Arl	Amine	Product	Ligand	Yield (%)
1		Et_2NH		**1b**	85%
2				**1a**	trace product
3				**1b**	86%
4				**1a**	trace product

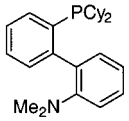
amination of aryl iodides at room temperature in good yield in the presence of stoichiometric 18-crown-6.[27]

In 1996, Hartwig described five examples in which aryl iodides were coupled with amines in high yield using 5 mol % of (DPPF)$PdCl_2$ at 100 °C.[26] He later reported that aryl iodides underwent the amination reaction at room temperature when the ligand D^{t}BPF was employed; however, the yields obtained were low in two of the three examples cited.[28] More recently, Nolan, in an application of Arduengo carbene-type ligands, has shown one instance of an aryl iodide undergoing the amination reaction in high yield at room temperature.[29]

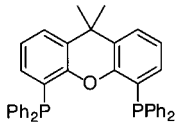
One aim of this study was to obtain general conditions, not requiring the use of toxic additives, for the cross-coupling of aryl iodides with all classes of amines. Another goal was to optimize mild conditions for the reaction of aryl iodides and amines containing base-sensitive functional groups. A class of biphenyl-based ligands (e.g., **1a**, **1b**, **2**) developed by our group[30,31] provided a starting point for these explorations. Xantphos (**3**), a chelating bisphosphine developed by van Leeuwen,[32] has been found to be a very effective ligand for amination[33−35] and amidation[36,37] reactions. Xantphos was screened alongside the biphenyl-based ligands in this study, and was the optimal ligand for certain substrate combinations.



1a: R=*t*-Bu
1b: R=Cy



2



3
xantphos

Results and Discussion

Most of the methodological advances in the palladium-catalyzed amination reaction have resulted from the development of increasingly effective ligands.[12,17−19,38] The monophosphinobiphenyl ligands developed in our group (e.g., **1a**, **1b**, **2**) are constituents of highly effective catalyst systems that have been applied in a number of palladium-catalyzed cross-coupling reactions, including Suzuki reactions,[31,39] amination of aryl halides,[31,40] diaryl ether formation,[41] and arylation of enolates.[42] These ligands are notable for being both bulky and electron-rich: their bulk speeds reductive elimination and favors coordinative unsaturation, and their high electron density facilitates oxidative addition.[39] Other ligands currently used for palladium-catalyzed amination (e.g., PCy_3,[43] P(*t*-Bu)$_3$,[38,44] PPF-OMe, and related ferrocenyl ligands,[28,45] palladacycles,[46] and carbene-type ligands[29,47]) share many of these attributes. One distinguishing feature of ligands **1a**,**b** and **2** is their exceptional air stability, even in solution.[40]

Initial studies on the amination of aryl iodides utilized ligand **1a** in light of its general utility for the amination of aryl bromides and aryl chlorides.[40] The results proved disappointing: low conversions were observed, and free ligand was often detectable by GC. A switch to the smaller cyclohexyl analogue, **1b**, provided more satisfactory results. Although in certain very facile reactions the

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(26) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218.
(27) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066−6068.
(28) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.
(29) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309.
(30) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.
(31) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413−2416.
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(33) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789−3790.
(34) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263.
(35) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019−6022.
(36) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37.
(37) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104.
(38) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620.
(39) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.
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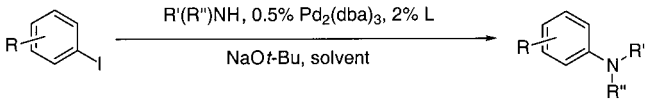
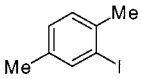
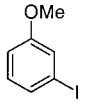
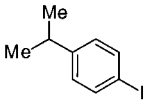
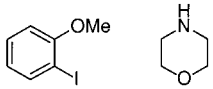
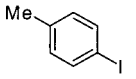
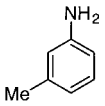
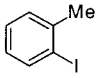
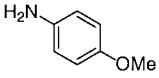
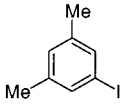
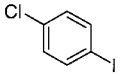
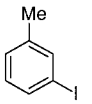
(43) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810.
(44) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370.
(45) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569.
(46) Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073−2074.
(47) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.

Table 2. Amination of Aryl Iodides with NaO*t*-Bu as Base[a]



Entry	Aryl	Amine	Ligand	Solvent[b]	Temp (°C)	Yield[c] (%)
1		*n*-HexNH$_2$	**1b**	a	100	70
2		BnNH$_2$	**1b**	a	100	79
3		MeN(H)Bn	**2**	a	60	89
4			**3**	b	60	94
5			**2**	b	45	99
6			**2**	b	45	99
7			**2**	c	RT	>99
8			**2**	c	RT	97
9		Ph$_2$NH	**2**	b	100	98

[a] Reaction times varied from 2 to 12 h. [b] Solvents: (a) 2:1 dioxane/*t*-BuOH, (b) dioxane, (c) tetrahydrofuran. [c] Yields refer to the average isolated yield of two runs. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

tert-butyl ligand was as effective, or almost as effective, as the cyclohexyl, in most cases **1b** performed significantly better. Two such examples are given in Table 1.

As further experiments revealed large disparities in reaction times, temperatures, and optimal ligand between substrates, a systematic optimization of the reaction conditions (including ligand, temperature, and catalyst loading) was undertaken for each type of amine being coupled.

A preliminary screen indicated the best ligand for a given class of amines. Initial experiments indicated that **1b**, **2**, and **3** were the most generally effective ligands; they were screened in each case. Other ligands, e.g., binaphthyl-based, ferrocenyl-based, and *tert*-butyl biphenyl phosphines, were periodically reexamined and found to be less effective than this basis set. Reactions were run in dioxane and in a 2:1 dioxane/*tert*-butyl alcohol mixture for the first round of experiments, as preliminary results indicated that dioxane was the most generally effective solvent (as in previous studies with aryl iodides[24]). The addition of *tert*-butyl alcohol led to enhanced reaction rates and conversion in most cases.[48] The use of nonpolar solvents resulted in slower conversion, whereas employing highly polar solvents such as NMP or DMA led to significant reduction of aryl iodide starting material to arene (presumably via β-hydride elimination and reductive elimination from the amido complex).

Once an optimal ligand was found, further screening was used to optimize reaction temperatures and solvents. The results are shown in Table 2. Yields are very good to excellent for most substrate combinations and higher than those obtained with the BINAP/18-crown-6 protocol. In most instances, the ligand of choice is **2**, but **1b** and **3** are useful in certain cases.

It is necessary to heat reactions involving primary aliphatic amines (entries 1 and 2) to 100 °C to achieve complete conversion. This may be due to the formation of catalytically inactive amido-bridged complexes and/or bis(amine) complexes.[49] The somewhat lower yields obtained with primary amines relative to other classes of amines stems in part from the formation of diarylated side products. When optimizing ligands, we sought to

(48) Harris, M. C.; Buchwald, S. L. Unpublished results.
(49) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534−3542.

minimize the extent of diarylation: **2** exhibited comparable reactivity to **1b** but led to higher incidences of diarylation, and hence **1b** was deemed the ligand of choice. The use of 1.4 equiv of amine (rather than 1.2 equiv) also helps to increase the ratio of desired monoarylated to undesired diarylated products.

The reactions of secondary acyclic amines are usually inefficient when BINAP is employed as ligand.[50] Nonetheless, with this improved protocol, they give the corresponding anilines in good yields upon heating to 60 °C (entry 3). Secondary cyclic amines (entry 4) were also coupled in high yield.

Particularly reactive substrates such as *N*-alkylanilines are converted readily at room temperature to afford the corresponding products in nearly quantitative yield (entries 7 and 8). Tetrahydrofuran was found to be the best solvent for this transformation. Although primary anilines can also be coupled at room temperature, it was found that gentle heating accelerates their reaction (entries 5 and 6).

The reaction of diphenylamine (entry 9) requires heating to 100 °C to achieve complete conversion. This may be a consequence of its relative bulk, which would inhibit its substitution of an iodide-bridged palladium dimer complex[51] or of a bulky palladium alkoxide complex.[52] An alternative explanation is that their reduced basicity inhibits the bonding to the Pd(II) center, which is necessary to facilitate their deprotonation.

The palladium-catalyzed cross-coupling of aryl iodides with amines in the presence of NaO*t*-Bu is an efficient and high-yielding reaction appropriate for the reactions of many substrates. However, NaO*t*-Bu is incompatible with many commonly encountered functional groups such as esters, enolizable ketones,[42] and other base-sensitive groups. An effort was thus made to extend the substrate scope of the process by the use of a milder base, as has been reported for the amination of aryl bromides and chlorides.[30,53] Among the bases screened were K_3PO_4, Cs_2CO_3, $CsHCO_3$, CsOAc, NaOAc, and proton sponge, the most effective of which was Cs_2CO_3. By contrast, when using our biphenyl-based ligands for the coupling of aryl bromides and chlorides, the best results were generally obtained with K_3PO_4. Accordingly, a ligand screen analogous to that described above for NaO*t*-Bu was undertaken with Cs_2CO_3.

Appropriate conditions were thus found for the functional group-tolerant reaction of various amines with aryl iodides in good to excellent yield, as shown in Table 3. Yields, although satisfactory, are somewhat lower than those obtained with NaO*t*-Bu. This can be attributed to the greater incidence of reduction observed under the mild base conditions. Elevated reaction temperatures (100 or 120 °C) are required in order to achieve high conversions with Cs_2CO_3. Reaction times are somewhat longer than those utilizing NaO*t*-Bu, although the protocol can be conveniently performed overnight. These differences may be a consequence of the lower solubility of Cs_2CO_3 in organic solvents relative to NaO*t*-Bu. The use of triethylamine as a cosolvent provided significant rate enhancements when running reactions with cesium carbonate (but not with NaO*t*-Bu). As with NaO*t*-Bu, ligand **2** is the most generally effective, although **3** is superior with primary and substituted aniline substrates.

Primary amines (entry 1) are readily coupled in good yields, although a higher catalyst loading (3% Pd) is required. As with NaO*t*-Bu, the requisite temperature is higher than for more activated substrates (*vide supra*). Secondary cyclic amines are coupled efficiently at 100 or 120 °C (entries 2 and 3).

Anilines and *N*-alkylanilines give high yields of the corresponding diarylamines when xantphos (**3**) is employed as ligand. Entry 3 of Table 3 (62%) can be compared to entry 4 of Table 2 (94%); the lower yield is due to the increased reduction to arene observed with Cs_2CO_3. The last two examples show that *N*-methylaniline reacts with activated and mildly activated aryl iodides in very good yield (comparable to those obtained with NaO*t*-Bu).

Two of the more difficult substrate classes, secondary acyclic amines and diarylamines, continue to give low conversions, decomposition products, and high incidences of reduction of aryl iodide to arene when Cs_2CO_3 is employed, despite much effort at optimization. The good yield obtained from the reaction of di(*n*-propyl)amine with 4-iodobenzophenone (entry 4) appears to be somewhat exceptional. Other substrates were less efficiently coupled. Efforts to find suitable conditions for these two classes of amine substrates are still in progress.

Conclusions

Conditions have been developed that allow for the coupling of aryl iodides with all classes of amines in good to excellent yields with NaO*t*-Bu as base. Milder conditions, utilizing Cs_2CO_3 as a base, have been optimized that permit the amination of aryl iodides in good yields in the presence of base-sensitive functional groups.

Experimental Section

General Considerations. All reactions were performed in oven- or flame-dried resealable Schlenk tubes under an atmosphere of argon. Aryl iodides were purchased from Aldrich Chemical Co., Lancaster Synthesis Limited or Trans World Chemicals Inc., and used without further purification. Amines were also purchased from commercial sources − those available in anhydrous form were used without further purification; all others were filtered through basic alumina prior to use. Tris-(dibenzylideneacetone)dipalladium(0) was purchased from Strem Chemical Company, as were ligands **1a** and **1b**. Ligands **2** and **3** were prepared following literature procedures.[30,32,54] Sodium *tert*-butoxide (Aldrich Chemical Co.) and cesium carbonate (Chemetall) were stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions were removed every few weeks and stored under air in a benchtop desiccator. Dioxane and 2-methyl-2-propanol were purchased anhydrous from Aldrich Chemical Co. and were used without further purification. Triethylamine was distilled under argon from calcium hydride and stored over potassium carbonate. THF was distilled under argon from sodium benzophenone ketyl. Yields in tables **2** and **3** refer to the average of two runs with isolated compounds of greater than 95% purity as determined by ^{1}H NMR and capillary GC. New compounds were characterized by combustion analysis; all elemental analyses were obtained from Atlantic Microlabs Incorporated, Norcross, GA. IR spectra

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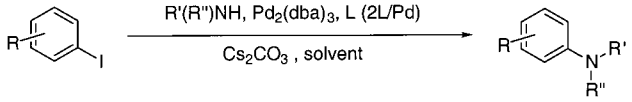
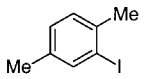
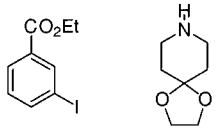
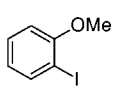
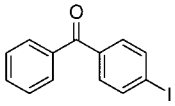
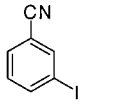
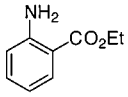
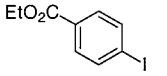
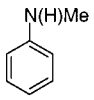
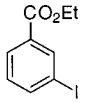
Table 3. Amination of Aryl Iodides with Cs_2CO_3 as Base[a]



Entry	Arl	Amine	mol% Pd	Ligand	Solvent[b]	Temp (°C)	Yield[c] (%)
1		*n*-HexNH$_2$	3	2	a	120	74
2			1	2	b	100	81
3			2	2	b	120	62
4		(*n*-Pr)$_2$NH	5	2	c	100	70
5			1	3	a	100	91
6			1	3	c	120	86
7			1	3	c	120	84

[a] All reactions were run overnight; reaction times were not minimized. [b] Solvents: (a) 2:1 dioxane/*t*-BuOH, (b) 1:1 dioxane/*t*-BuOH, (c) 2:1 dioxane/Et_3N. [c] Yields refer to the average isolated yield of two runs. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

of neat samples were acquired with the DiComp probe of an ASI REACTIR in situ IR instrument.

General Procedure. $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 1 mol %), ligand **2** (7.9 mg, 0.02 mmol, 2 mol %), and base were weighed in air and transferred to a flame-dried resealable Schlenk tube. For Table 2, the base used was NaO*t*-Bu (135 mg, 1.4 mmol) and for Table 3 the base used was Cs_2CO_3 (456 mg, 1.4 mmol). Amine (1.2 mmol) and aryl iodide (1.0 mmol), if solid, were added at this point. The tube was then evacuated and backfilled with argon. The flask was capped with a rubber septum under an argon purge, and the liquid reagents (amine and/or aryl iodide) added. The sides of the flask were rinsed with solvent (3.0 mL), and the septum replaced by a Teflon screwcap. The Schlenk tube was then sealed and stirred at the appropriate temperature. When GC analysis indicated disappearance of aryl iodide, the reaction mixture was cooled to room temperature, diluted with ether, and filtered through a plug of Celite. The crude product was concentrated and purified directly by flash chromatography on silica gel.

***N*-(2,5-Xylyl)hexylamine (Table 2, Entry 1).**[24] The general procedure, with 0.02 mmol (7.0 mg) of ligand **1b**, 1.0 mmol (145 mL) of 2-iodo-*p*-xylene, and 1.4 mmol (185 mL) of *n*-hexylamine in 2:1 dioxane/*t*-BuOH at 100 °C, yielded 159 mg (77%) of a yellow oil.

***N*-(3-Methyoxyphenyl)benzylamine (Table 2, Entry 2).** The general procedure, with 0.02 mmol (7.0 mg) of ligand **1b**, 1.0 mmol (120 mL) of 3-iodoanisole, and 1.4 mmol (153 mL) of benzylamine in 2:1 dioxane/*t*-BuOH, yielded 166 mg (78%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 7.10−7.04 (app t, 1 H), 6.29−6.23 (m, 2H), 6.19−6.18 (m, 1H), 4.31 (s, 2H), 4.04 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 149.6, 139.4, 130.1, 128.8, 127.6, 127.4, 106.1, 102.8, 99.0, 55.3, 48.6; IR (neat, cm^{-1}) 3415, 3062, 3029, 3000, 2954, 2834, 1613, 1598, 1495, 1453. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.96; H, 7.17.

***N*-Benzyl-*N*-methyl-4-isopropylaniline (Table 2, Entry 3).** The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (166 mL) of 4-iodoisopropylbenzene, and 1.2 mmol (155 mL) of *N*-methylbenzylamine in 2:1 dioxane/*t*-BuOH at 60 °C, yielded 210 mg (88%) of an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 5H), 7.10−7.06 (m, 2H), 6.73−6.68 (m, 2H), 4.48 (s, 2H), 2.97 (s, 3H), 2.88−2.75 (sept, 1H, J = 6.9 Hz), 1.22−1.20 (d, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 139.5, 137.1, 128.6, 127.1, 127.0, 126.9, 112.6, 57.3, 38.8, 33.3, 24.5; IR (neat, cm^{-1}) 3029, 2958, 2927, 2867, 2809, 1615, 1519, 1495, 1453. Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.84. Found: C, 85.08; H, 8.89.

***N*-(2-methoxyphenyl)morpholine (Table 2, Entry 4).** The general procedure, with 0.02 mmol (11.6 mg) of ligand **3**, 1.0 mmol (130 mL) of 2-iodoanisole, and 1.2 mmol (105 mL) of morpholine in dioxane at 60 °C, yielded 184 mg (95%) of a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04−7.00 (m, 1H), 6.94−6.93 (m, 2H), 6.89−6.87 (m, 1H), 3.91−3.86 (m, 4H), 3.87 (s, 3H), 3.08−3.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3,

141.1, 123.3, 121.1, 118.1, 111.3, 67.4, 55.6, 51.4; IR (neat, cm^{-1}) 3062, 2956, 2854, 2833, 2817, 1594, 1499, 1447, 1378, 1299, 1237. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7,82. Found: C, 68,13; H, 7.79.

3-Methyl-4′-methyldiphenylamine (Table 2, Entry 5). The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (218 mg) of 4-iodotoluene, and 1.2 mmol (129 mL) of *m*-toluidine in dioxane at 45 °C, yielded 198 mg (>99%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, 1H, J = 7.5 Hz), 7.12−7.10 (d, 2H, J = 8.0 Hz), 7.03−7.01 (m, 2H), 6.86−6.84 (m, 2H), 6.74−6.72 (d, J = 7.0 Hz), 5.58 (br s, 1H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 140.4, 139.3, 130.9, 129.9, 129.3, 121.3, 119.0, 114.1, 21.8, 21.0; IR (neat, cm^{-1}) 3394, 3025, 2919, 2861, 1605, 1590, 1515, 1490, 1318, 1304. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 85.01; H, 7.72.

2-Methyl-4′-methoxydiphenylamine (Table 2, Entry 6). The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (127 mL) of 2-iodotoluene, and 1.2 mmol (148 mg) of *p*-anisidine in dioxane at 45 °C, yielded 211 mg (99%) of a yellow-white solid: mp 78−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.16 (m, 1H), 7.11−7.06 (m, 1H), 7.05−7.01 (m, 3H), 6.89−6.86 (m, 2H), 6.84−6.81 (td, 1H, J = 7.3 Hz, 1.2 Hz), 5.23 (br s, 1 H), 3.82 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 143.4, 136.3, 130.8, 126.9, 125.3, 122.3, 120.1, 115.2, 114.8, 55.8, 18.1; IR (neat, cm^{-1}) 3394, 2968, 2927, 2834, 1584, 1505, 1478, 1468, 1453, 1312, 1293, 1237. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 79.04; H, 7.13.

***N*-(3,5-Xylyl)-*N*-ethylaniline (Table 2, Entry 7).**[45] The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (144 mL) of 5-iodo-*m*-xylene, and 1.05 mmol (132 mL) of *N*-ethylaniline in THF at rt, yielded 226 mg (>99%) of an orange oil.

***N*-Methyl-*N*-phenyl-4-chloroaniline (Table 2, Entry 8).**[24] The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (238 mg) of 1-chloro-4-iodobenzene, and 1.0 mmol (108 mL) of *N*-methylaniline in THF at rt yielded 211 mg (97%) of a yellow oil.

***N*-(3-Methylphenyl)diphenylamine (Table 2, Entry 9).**[55] The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (128 mL) of 3-iodotoluene, and 1.05 mmol (178 mg) of diphenylamine in 0.5 M dioxane at 80 °C, yielded 254 mg (98%) of a white solid: mp 62−65 °C (lit.[55] mp 66−67 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.22 (m, 4H), 7.15−7.12 (m, 1H), 7.09−7.06 (m, 4H), 7.01−6.98 (m, 2H), 6.90 (m, 1H), 6.89−6.87 (m, 1H), 6.84−6.83 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.8, 139.2, 129.3, 129.1, 125.1, 124.2, 123.8, 122.6, 121.7, 21.7.

***N*-(2,5-Xylyl)hexylamine (Table 3, Entry 1).**[24] The general procedure, with 0.0075 mmol (6.9 mg) of $Pd_2(dba)_3$, 0.03 mmol (11.8 mg) of ligand **2**, 0.5 mmol of 2-iodo-*p*-xylene, and 0.7 mmol (92 mL) of *n*-hexylamine in 1.5 mL of 2:1 dioxane/*t*-BuOH at 120 °C, yielded 81 mg (79%) of a yellow oil.

***N*-(3-Carbethoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]-decane (Table 3, Entry 2).** The general procedure, with 0.02 mmol (7.9 mg) of ligand **2**, 1.0 mmol (165 mL) of ethyl 3-iodobenzoate, and 1.2 mmol (154 mL) of 1,4-dioxa-8-azasprio-[4.5]decane in 2.0 mL of 1:1 dioxane/*t*-BuOH at 100 °C, yielded 237 mg (81%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.51−7.48 (dd, 1H, J = 7.6 Hz, 1.0 Hz), 7.32−7.26 (m, 1H), 7.13−7.09 (dt, 1H, J = 82 Hz, 1.3 Hz), 4.40−4.32 (qd, 2H, J = 7.1 Hz, 1.0 Hz), 4.00 (s, 3H), 3.37 (t, 4H, J = 5.5 Hz), 1.84 (t, 4H, J = 5.5 Hz), 1.41 (td, 3H, J = 7.1 Hz, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 150.9, 131.4, 129.1, 120.9, 120.4, 117.4, 107.2, 64.6, 61.3, 47.8, 34.7, 14.7; IR (neat, cm^{-1}) 2960, 2933, 2885, 2834, 1713, 1600, 1580, 1492, 1443. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 66.12; H, 7.15.

***N*-(2-Methoxyphenyl)morpholine (Table 3, Entry 3).** The general procedure, using 0.01 mmol (9.2 mg) of $Pd_2(dba)_3$, 0.04 mmol (15.7 mg), 1.0 mmol (130 mL) of 2-iodoanisole, and 1.2 mmol (105 mL) of morpholine in 2.0 mL of 1:1 dioxane/*t*-BuOH at 120 °C, yielded 123 mg (64%) of a yellow oil.

***N*-(4-Benzoylphenyl)dipropylamine (Table 3, Entry 4).** The general procedure, with 0.025 mmol (11.4 mg) of $Pd_2(dba)_3$, 0.10 mmol (19.7 mg) of ligand **3**, 0.5 mmol (154 mg) of 4-iodobenzophenone, and 0.6 mmol (82 mL) of di(*n*-propyl)-amine in 1.5 mL of 2:1 dioxane/Et_3N at 100 °C yielded 101 mg (72%) of a yellow solid: mp 96−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.73 (m, 2H), 7.73−7.70 (m, 2H), 7.54−7.41 (m, 3H), 6.63−6.60 (m, 2H), 3.35−3.29 (t, 4H, J = 7.7 Hz), 1.70−1.60 (m, 4H), 0.98−0.93 (t, 6H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 151.6, 139.5, 133.1, 131.0, 129.5, 128.1, 124.0, 110.3, 53.0, 20.7, 11.7; IR (neat, cm^{-1}) 2960, 2931, 2873, 1636, 1584, 1574, 1542, 1524. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.0; H, 8.24. Found: C, 80.81; H, 8.24.

3-Cyano-2′carboethyoxydiphenylamine (Table 3, Entry 5). The general procedure, with 0.02 mmol (11.6 mg) of ligand **3**, 1.0 mmol (229 mg) of 3-iodobenzonitrile, and 1.05 mmol (155 mL) of ethyl 2-aminobenzoate in 2:1 dioxane/*t*-BuOH at 100 °C, yielded 242 mg (91%) of a white solid: mp 78−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.04−8.01 (ddd, 1H, J = 8.0 Hz, 1.7 Hz, 0.5 Hz), 7.53−7.52 (m, 1H), 7.45−7.37 (m, 3H), 7.32−7.26 (m, 2H), 6.89−6.83 (td, 1H, J = 7.5 Hz, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 146.0, 142.2, 134.2, 131.9, 130.4, 126.1, 125.4, 123.6, 119.0, 114.7, 113.9, 113.4, 61.2, 14.6; IR (neat, cm^{-1}) 3294, 3245, 3188, 2977, 2231, 1679, 1603, 1571, 1453. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30. Found: C, 71.89; H, 5.43.

***N*-(4-Carbethoxyphenyl)-*N*-methylaniline (Table 3, Entry 6).** The general procedure, with 0.02 mmol (11.6 mg) of ligand **3**, 1.0 mmol (171 mL) of ethyl 4-iodobenzoate, and 1.0 mmol (108 mL) of *N*-methylaniline in 2:1 dioxane/Et_3N at 120 °C, yielded 234 mg (92%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.84 (m, 2H), 7.41−7.35 (m, 2H), 7.22−7.16 (m, 3H), 6.79−6.74 (m, 2H), 4.35−4.28 (q, 2H, J = 7.2 Hz), 3.60 (s, 3H), 1.38−1.34 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.5, 147.6, 131.1, 129.9, 125.9, 125.4, 119.7, 114.0, 60.5, 40.5, 14.8; IR (neat, cm^{-1}) 3060, 2981, 2935, 2904, 2819, 1702, 1609, 1590, 1515, 1493, 1351. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.44; H, 6.89.

***N*-(3-Carbethoxyphenyl)-*N*-methylaniline (Table 3, Entry 7).** The general procedure, with 0.02 mmol of ligand **3** (11.6 mg), 1.0 mmol (165 mL) of ethyl 3-iodobenzoate, and 1.0 mmol (108 mL) of *N*-methylaniline in 2:1 dioxane/Et_3N at 120 °C, yielded 217 mg (85%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (app. t, 1H), 7.60−7.56 (m, 1H), 7.33−7.25 (m, 3H), 7.15−7.11 (ddd, 1H, J = 8.2 Hz, 2.5 Hz, 1.1 Hz), 7.08−7.00 (m, 3H), 4.36 (q, 2H, J = 7.1 Hz), 3.35 (s, 3H), 1.38 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 149.2, 148.7, 131.7, 129.6, 129.1, 123.7, 122.7, 122.1, 121.7, 119.7, 61.3, 40.7, 14.7; IR (neat, cm^{-1}) 3064, 3037, 2981, 2904, 2815, 1717, 1592, 1582, 1495, 1443. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.49; H, 6.68.

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