Use of Polymer-Supported Dialkylphosphinobiphenyl Ligands for Palladium-Catalyzed Amination and Suzuki Reactions

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The preparations of polymer-supported dialkylphosphinobiphenyl ligands (**3**) are reported. A palladium catalyst based on ligand **3a** is active for amination and Suzuki reactions using unactivated aryl iodides, bromides, or chlorides. Filtration of the catalyst from the reaction mixture allows for simplified product isolation via an aqueous workup. The resin-bound catalyst can be recycled without additional palladium in both the amination and Suzuki reactions.

Introduction

Palladium-catalyzed coupling reactions have become a common method for the synthesis of aromatic amines and biaryls.[1,2] The introduction of dialkylphosphinobiphenyl ligands has enhanced the efficiency of various C−C and C−N bond-forming reactions by providing access to highly active palladium catalysts.[3] These catalysts allow for sterically congested Suzuki couplings, room temperature cross-couplings of aryl bromides or chlorides, and the use of low catalyst loading.[4] Such catalysts have also led to efficient systems for the cross-coupling of various aryl bromides, chlorides, and triflates with a variety of amines at room temperature or above.[5] These dialkylphosphinobiphenyl ligands are now either commercially available[6] or readily prepared in a one-pot procedure.[7] To further expand the utility of these active phosphine ligands, we considered solid-supported catalysts, whereby the ease of product isolation, the purity of the crude product, and the potential to recycle the catalyst can be major advantages over homogeneous systems.

Because of the need for more environmentally benign chemistry and the desire to develop simplified protocols for rapid screening methods, there is a demand for highly active heterogeneous catalysts. Although increasingly popular on a research scale, many palladium-catalyzed processes have not found significant use on an industrial scale due to their high cost and the difficulty in removal of palladium and ligand. Various types of solid-supported catalysts have been prepared.[8−10] Polymer-supported palladium catalysts have found applications in allylic substitutions,[11,12] hydrogenations,[11b,13] polymerizations,[14] enantioselective reactions,[12,15] and cross-coupling reactions.[11d,16] Several reports have been published describing polymer-supported C−C bond-forming reactions such as the Heck and Suzuki reactions.[11e−g,14c,17,18] However, most of these examples utilize reactive and costly aryl iodides or bromides as substrates. Initial findings

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(2) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2.

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(5) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(6) 2-Dicyclohexylphosphinobiphenyl, 2-di-*tert*-butylphosphinobiphenyl, and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl are commercially available from Strem Chemicals, Inc.

(7) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

(8) For reviews on functionalized polymers, see: (a) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035, and references therein.

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(10) For a review on the use of soluble polymers, see: Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.

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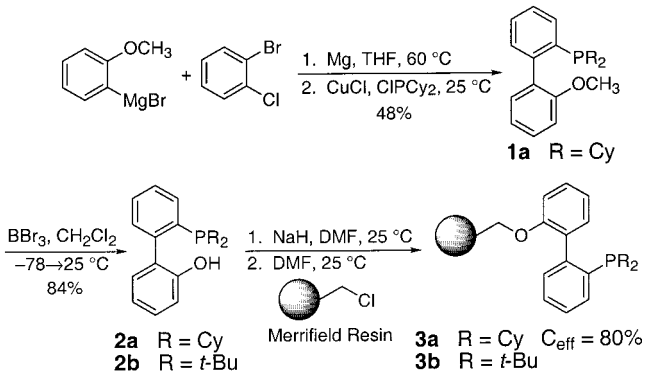
Scheme 1



by Buchmeiser and Wurst describe aryl chloride activation in the Heck reaction between chlorobenzene or 4-chloroacetophenone and styrene (89% and 96% conversion, respectively) in the presence of tetrabutylammonium bromide and a polymer-supported palladium catalyst at high temperature (140 °C).[14c,19] However, a general and practical solid-supported palladium catalyst system that can utilize readily available and inexpensive aryl chlorides as substrates still remains a goal.[20]

As our group and others have shown that the use of electron-rich phosphine ligands in palladium-catalyzed C−C and C−N bond-forming reactions allows for an increase in aryl halide substrate scope,[21] we initiated a program to develop heterogeneous catalysts based on the incorporation of dialkylphosphinobiphenyl ligands into polymer supports as leading to highly practical and general catalysts. On the basis of our previous results with the related homogeneous catalysts, we would also expect such polymer-supported ligands to be air stable. A few examples of polymer-bound electron-rich phosphines have been published; complexes of these ligands catalyzed olefin metathesis,[14a] the Heck reaction of aryl iodides,[17d] and the hydrogenation of enamides.[13a] Herein we disclose the synthesis of polymer-supported dialkylphosphinobiphenyl-based catalysts and their success in the Suzuki and amination reactions of unactivated aryl iodides, bromides, and chlorides.

Results and Discussion

Our initial work focused on the use of a short ether linkage to attach the biphenylphosphine to the polymer backbone. Polymer-bound dialkylphosphinobiphenyl ligand **3a** was readily prepared utilizing recent methodology described from these laboratories.[7] The biphenyl framework, 2-dicyclohexylphosphino-2′-methoxybiphenyl (**1a**), was synthesized by the reaction of 2-methoxyphenylmagnesium bromide with benzyne and subsequent addition of chlorodicyclohexylphosphine in 48% overall yield (Scheme 1). Deprotection of the aryl methyl ether with boron tribromide then led to 2-dicyclohexylphosphino-2′-hydroxybiphenyl (**2a**) in 84% crude yield. Care was taken to avoid the presence of oxygen or basic conditions, both of which seemed to facilitate oxidation of the ligand. Deprotonation of the phenol with sodium hydride in *N*,*N*-dimethylformamide followed by addition of the Merrifield resin (1% cross-linked with divinylbenzene, 200−400 mesh size) afforded the resin-bound dicyclohexylphosphine ligand **3a** with an average coupling efficiency of 80%.[22] Once attached to the solid support, the ligand is air stable. Ligands **2a** and **2b** could also be prepared in a one-step procedure from dibenzofuran according to the method of Heinicke and co-workers.[23] The di-*tert*-butylphosphine ligand **3b** could only be prepared using a dilute solution of 2-di-*tert*-butylphosphino-2′-hydroxybiphenyl (**2b**) provided by this alternative method. However, subsequent reactions utilizing ligand **3b** indicated no advantage as compared to ligand **3a**, and due to its more difficult preparation, it was not pursued further. The polymer-supported phosphine ligands **3** were characterized by gel phase ^{31}P NMR (Figure 1)[24] and by phosphorus elemental analysis.

Initial studies with polymer-supported dicyclohexylphosphine ligand **3a** revealed that premixing of the catalyst system is essential for high catalytic activity. Palladium-catalyzed amination and Suzuki reactions were successful when resin **3a** was allowed to stir and swell in the presence of the palladium source in solvent for 30−60 min prior to addition of the remaining reactants. As visualized in Figure 2, the yellow color of the palladium solution transferred to the polymer beads over the course of 30 min, leaving the solution colorless, likely an indication of the formation of a palladium−phosphine complex. That such a complex is formed on the resin and acts as a catalyst is further supported by the following experiments. Removal of the solution from the resin (after premixing with either $Pd(OAc)_2$ or $Pd_2(dba)_3$) followed by addition of fresh solvent and the remaining reactants to the flask provided results similar to those when the original solution was left untouched. Similarly, control experiments performed with resin containing no phosphine (prepared from 2-hydroxybiphenyl and the Merrifield resin in the same manner as ligands **3**) led only to trace amounts of product formation in the palladium-catalyzed amination and Suzuki reactions.

Use of the solid-supported electron-rich phosphine ligand **3a** led to an active catalyst system for the palladium-catalyzed amination reaction.[25] Under standard conditions using typically only 1.0 mol % of palladium, primary amines, secondary cyclic and acyclic amines, and anilines were all coupled successfully with various unactivated or deactivated aryl halides in very good yields (Table 1). Furthermore, aryl chlorides could now be successfully utilized as substrates (entries 5, 11−13), something which had not previously been possible with the other reported polymer-supported phosphine- or carbene-based ligands for palladium-catalyzed aryl halide activation.[11d−f,17,18] In fact, similar reaction conditions were used in these amination reactions with

(19) Two examples of ArCl activation (<40%) with heterogeneous Pd catalysts have been published, see: (a) Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921. (b) Djakovitch, L.; Heise, H.; Köhler, K. *J. Organomet. Chem.* **1999**, *584*, 16.

(20) The Suzuki reaction of aryl chlorides using Ni/C (5−10 mol %) has been published. However, catalyst activation by added triphenylphosphine (4 equiv) is required. Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139.

(21) For a discussion of this, see: (a) Buchwald, S. L.; Fox, J. M. In *The Strem Chemiker*; Strem Chemicals, Inc.: Newburyport, MA, 2000; Vol. XVIII, No. 1, and references therein. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020, and references therein.

(22) Coupling efficiency is calculated as the weight gained by the resin divided by the expected weight gain.

(23) Kadyrov, R.; Heinicke, J.; Kindermann, M. K.; Heller, D.; Fischer, C.; Selke, R.; Fischer, A. K.; Jones, P. G. *Chem. Ber.* **1997**, *130*, 1663.

(24) (a) Johnson, C. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253. (b) Lorgé, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem.* **1999**, *1*, 25.

(25) An example of aryl bromide amination using a polymer-supported Pd catalyst has been published, see ref 14c.

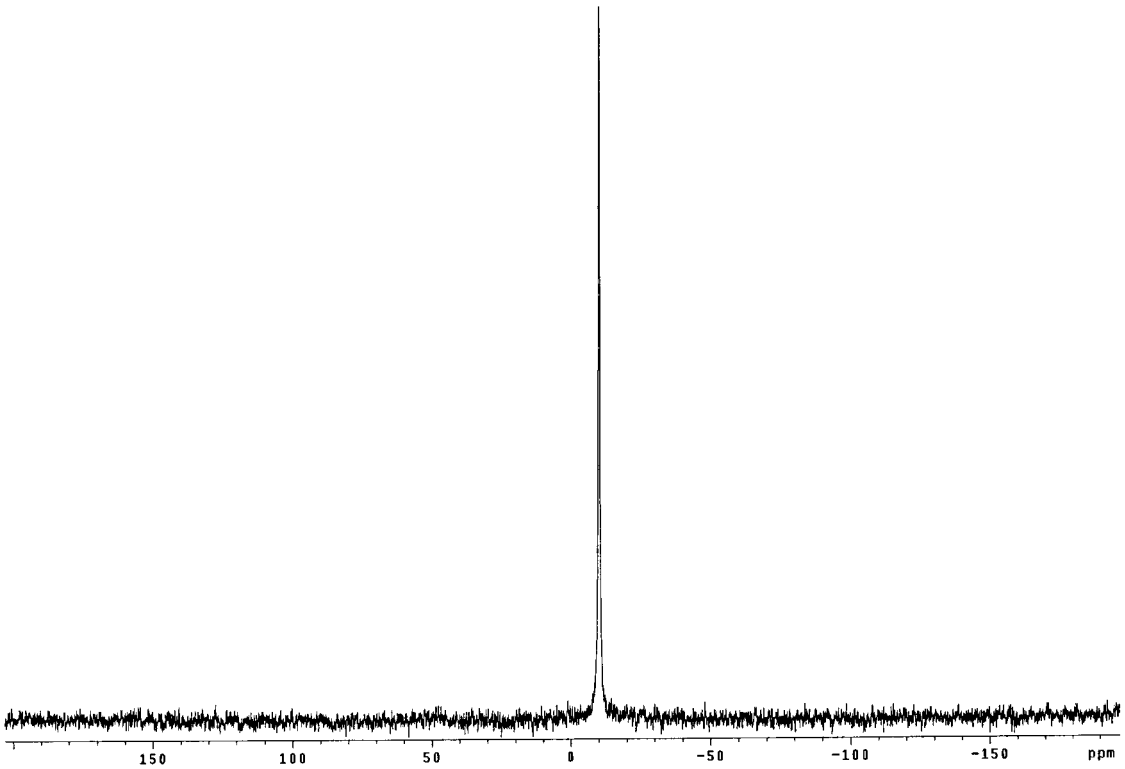


Figure 1. Gel phase ^{31}P NMR (121 MHz, C_6D_6) spectrum of ligand **3a**. Spectrum was processed with a line broadening of 10 Hz.

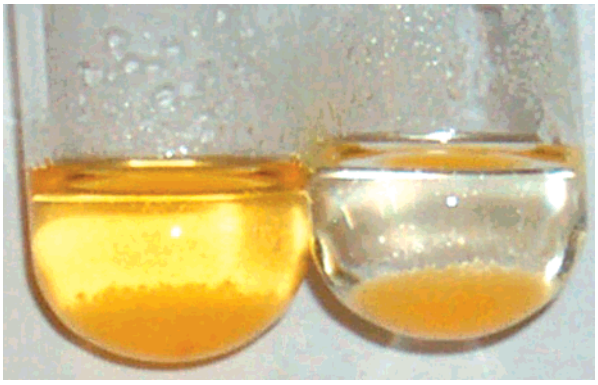


Figure 2. A visual description of the premixing protocol. Both test tubes contain identical solutions of $Pd(OAc)_2$ (15.0 μmol) and ligand **3a** (18.8 μmol, 200−400 mesh size) in THF (1.0 mL). The solution on the left has been standing for 5 min, whereas the solution on the right has been stirring for 30 min.

comparable results for aryl iodides, bromides, or chlorides. Furthermore, the lack of byproduct formation and the use of a polymer-supported catalyst allowed for facile product isolation. The resin was simply separated from the reaction mixture by filtration, and the product was isolated following an aqueous workup. As such, the products were judged to be of >95% purity by standard analytical methods.[26] Filtered reaction mixtures were also subjected to analysis by ^{31}P NMR, whereby no phosphorus peaks were detected.

Initial results demonstrated the use of palladium-activated ligand **3a** to be effective for the cross-coupling of aryl bromides with arylboronic acids using potassium fluoride or potassium phosphate as the base in a tetrahydrofuran solution. However, analysis of filtered reaction mixtures by ^{31}P NMR indicated that there was in fact phosphine cleavage from the resin under these reaction conditions in up to 20% in the presence of 2.0 mol % of palladium. Further experiments indicated that no phosphine leaching was occurring when the reaction conditions consisted of cesium carbonate as the base and $Pd_2(dba)_3$ as the palladium source.

Using these modified Suzuki reaction conditions, arylboronic acids were successfully cross-coupled with a number of unactivated aryl halides with solid-supported ligand **3a** and no more than 1.0 mol % of palladium (Table 2). Aryl iodides and bromides required even less catalyst. Although aryl chlorides were successfully utilized as starting materials, competitive hydrolytic deboronation of the arylboronic acid was observed.[27] Increased amounts of boronic acid (1.5−3.0 equiv) were often necessary to drive the reactions to completion. This did not lead to increased byproduct formation; negligible amounts of biaryl products were formed and the deboronation products were removed in vacuo. Once again, the products were isolated in excellent yield upon filtration and aqueous workup and were determined to be of >95% purity by standard analytical methods.[26]

The ability to successfully recycle a heterogeneous catalyst system is of great importance. The catalyst derived from ligand **3a** and $Pd(OAc)_2$ or $Pd_2(dba)_3$ can be recycled in both the amination and Suzuki reactions without addition of palladium (Table 3).[28,29] Catalyst activity and reaction rate were typically unaffected until

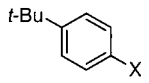
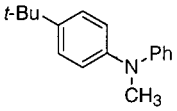
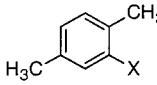
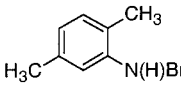
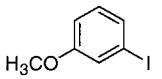
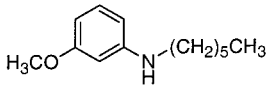
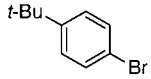
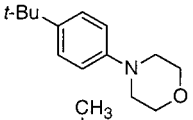
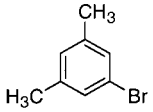
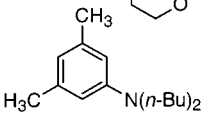
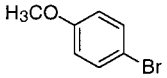
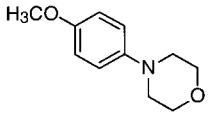
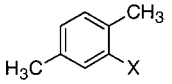
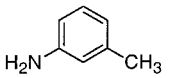
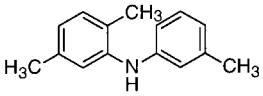
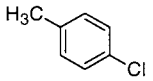
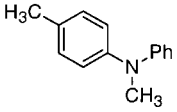
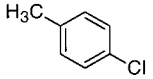
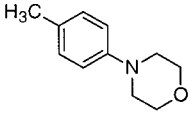
(26) In most cases, ^1H NMR, GC, ^{13}C NMR, FTIR, and EA data were obtained.

(27) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(28) Recycling experiments were conducted with a larger size (100−200 mesh) resin, prepared as shown in Scheme 1, due to its greater ease of use.

(29) The reaction mixture was diluted with ether and the resin was filtered, washed with water, *tert*-butyl alcohol, and ether, and dried in vacuo prior to the next reaction.

Table 1. Amination Reactions Using Ligand 3a[a]

Entry	Aryl Halide		Amine	Pd (mol%)	Product	Yield
1[b]		X = I	$HN(CH_3)Ph$	1.0		95%
2		X = Br		1.0		93%
3		X = I		1.0		91%
4[c]		X = Br	H_2NBn	2.0		94%
5		X = Cl		1.0		94%
6[d]			$H_2N(CH_2)_5CH_3$	1.0		84%[e]
7				1.0		90%
8			$HN(n\text{-}Bu)_2$	1.0		79%
9				1.0		84%
10[c]		X = Br		1.0[f]		99%
11[c]		X = Cl		1.5[f]		95%
12[b]			$HN(CH_3)Ph$	1.0		92%
13				1.0		90%

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.3 equiv of amine, 1.5 equiv of NaO*t*-Bu, catalytic $Pd(OAc)_2$, ligand **3a** (1.3:1 L:Pd), toluene (0.5 M solution), 80 °C, 15−20 h (reaction times have not been minimized). Yields (average of two or more experiments) represent isolated yields of products estimated to be >95% pure as indicated by ^1H NMR, GC, and EA. [b] THF was used as the solvent at 65 °C. [c] The reaction temperature was increased to 100 °C. [d] A total of 3.0 equiv of amine was used. [e] The product was isolated from 3% of the diarylamine byproduct by flash chromatography. [f] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$.

the fourth consecutive reaction. Although the reactions became impractical due to extended reaction times, the absence of byproducts would have allowed for additional recycles. The use of the aqueous or alcoholic workup to remove inorganic solids from the reaction mixture may lead to modification of the palladium−phosphine complex and catalyst deactivation.

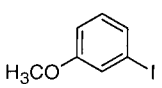
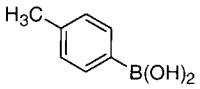
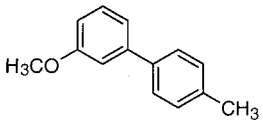
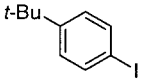
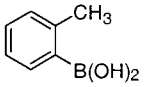
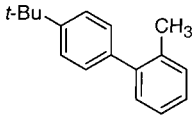
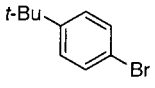
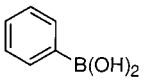
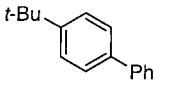
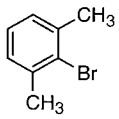
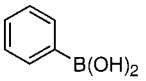
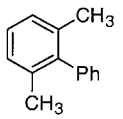
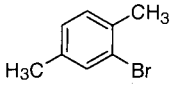
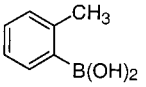
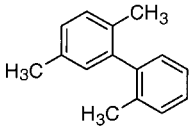
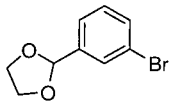
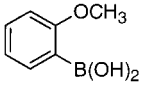
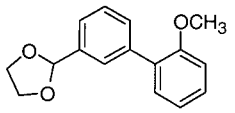
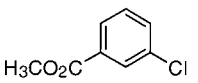
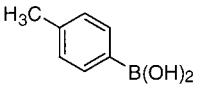
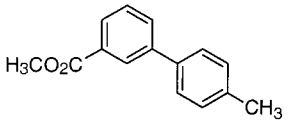
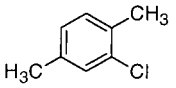
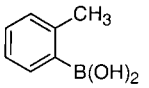
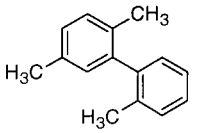
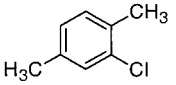
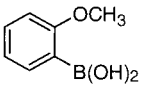
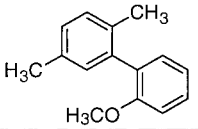
Conclusion

In summary, we have ligated a dialkylphosphinobiphenyl ligand to a polymer support and have demonstrated its utility in palladium-catalyzed cross-coupling reactions. In combination with a palladium source, ligand **3a** forms an active resin-bound catalyst for amination and Suzuki reactions, allowing for simplified product purification and a product devoid of phosphine contamination. Reactions using the electron-rich phosphine ligand **3a** are the first successful examples of the use of aryl chloride substrates with a solid-supported catalyst for amination or Suzuki reactions. The catalyst derived from ligand **3a** can also be recycled a limited number of times without additional palladium for both the amination and Suzuki reactions. Efforts are currently underway in our laboratories to develop other palladium-based heterogeneous catalyst systems that maintain excellent C−C and C−N bond-forming activity but demonstrate improved recycling ability.

Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere in oven-dried glassware. Toluene was distilled under nitrogen from molten sodium. THF was distilled under argon from sodium benzophenone ketyl or purchased anhydrous from Sigma-Aldrich Chemical Co. Dichloromethane and *N*,*N*-dimethylformamide were purchased anhydrous from Sigma-Aldrich. Copper(I) chloride, chlorodicyclohexylphosphine, palladium acetate, and tris(dibenzyli-

Table 2. Suzuki Cross-Coupling Reactions Using Ligand 3a[a]

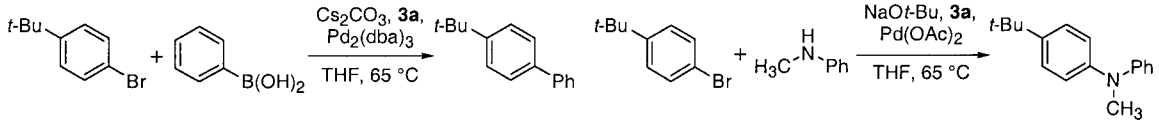
Entry	Aryl Halide	Boronic Acid	Pd (mol%)	Product	Yield
1			0.2		94%
2			0.3		98%
3			0.5		95%
4			0.5		92%
5[b]			0.5		99%
6			0.7		92%
7[b]			0.5		92%
8[c]			1.0		99%
9[c]			1.0		92%[d]

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.2 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, catalytic $Pd_2(dba)_3$, ligand **3a** (1.3−1.5:1 L:Pd), THF (0.5 M solution), 65 °C, 17−21 h (reaction times have not been minimized). Yields (average of two or more experiments) represent isolated yields of products estimated to be >95% pure as indicated by ^{1}H NMR, GC, and EA. [b] A total of 1.5 equiv of boronic acid was used. [c] A total of 3.0 equiv of boronic acid was used. [d] One of the two reaction mixtures proceeded to ~98% conversion.

deneacetone)dipalladium(0) were purchased from Strem Chemicals, Inc. Merrifield's peptide resin (1% cross-linked with divinylbenzene, 100−200 or 200−400 mesh) and 2-methoxyphenylmagnesium bromide were purchased from Sigma-Aldrich. Aryl halides were purchased from commercial sources and were used as received. Amines were purchased from commercial sources and were passed through a short column of basic alumina prior to use. Boronic acids were purchased from Sigma-Aldrich or Strem Chemicals. Sodium *tert*-butoxide was purchased from Sigma-Aldrich; the bulk of this material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small (1−2 g) portions were removed from the glovebox in glass vials and stored in a desiccator for use up to 1 week. Cesium carbonate was obtained from Chemetall Chemical Products, Inc.; the bulk of this material was stored under nitrogen in a glovebox. Portions (~10 g) were removed from the glovebox in glass vials and stored in a desiccator for extended use. Standard elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, and phosphorus elemental analyses were performed by E&R Microanalytical Laboratory, Parsippany, NJ. The procedures described in this section are representative, and thus yields may differ from those given in Tables 1−3.

2-Dicyclohexylphosphino-2′-methoxybiphenyl (1a). Tetrahydrofuran (45.0 mL) was added to a 500 mL flask charged with magnesium (1.22 g, 50.0 mmol, 1.0 equiv). 2-Methoxyphenylmagnesium bromide (55 mL of a 1.0 M solution in THF, 55.0 mmol, 1.1 equiv) and 1,2-bromochlorobenzene (5.8 mL, 50.0 mmol, 1 equiv) were added sequentially to the reaction mixture. A reflux condenser was fitted to the flask, and the reaction mixture was heated at 60 °C. After 2.5 h, the mixture was cooled to room temperature. Copper(I) chloride (5.94 g, 60.0 mmol, 1.2 equiv) and then chlorodicyclohexylphosphine (12.3 mL, 55.0 mmol, 1.1 equiv) were added, and the reaction mixture was stirred at room temperature. After 16 h, the mixture was filtered and rinsed with hexanes (2 × 50 mL). The solid was transferred to a 500 mL Erlenmeyer flask. Ether (150 mL) and saturated aqueous ammonia solution (200 mL) were added, and the mixture was stirred for 2 h. The mixture was transferred to a separatory funnel with a saturated

Table 3. Catalyst Recycling Experiments[a]



Entry	Pd (mol%)	Time	Conversion	Yield
1	2.0	20 h	100%	98%
2	0	24 h	100%	92%
3	0	24 h	96%	86%
4	0	87 h	96%	83%

Entry	Pd (mol%)	Time	Conversion	Yield
1	1.5	21 h	100%	93%
2	0	24 h	100%	94%
3	0	24 h	100%	97%
4	0	47 h	97%	89%
5	1.5	45 h	97%	88%

[a] Reaction conditions (Suzuki): 1.0 equiv of aryl bromide, 1.2 equiv of boronic acid, 2.0 equiv of Cs_2CO_3, stated amount of $Pd_2(dba)_3$, ligand **3a** (2.6 mol %), THF (0.5 M solution), 65 °C. The same resin was used for each entry. Reaction conditions (amination): 1.0 equiv of aryl bromide, 1.3 equiv of amine, 1.5 equiv of NaO*t*-Bu, stated amount of $Pd(OAc)_2$, ligand **3a** (2.0 mol %), THF (0.5 M solution), 65 °C. The same resin was used for each entry. Yields refer to isolated product estimated to be >95% pure as indicated by ^{1}H NMR and GC (and EA, first entry only).

aqueous ammonia solution (500 mL) and ether (200 mL). The layers were separated, and the aqueous layer was further extracted with ether (2 × 200 mL). The combined organic layers were washed with a saturated aqueous ammonia solution (2 × 150 mL) and brine (150 mL), dried over sodium sulfate, and concentrated in vacuo. Recrystallization of the residue with hot methanol provided the title compound as a white solid (9.09 g, 48%) in two crops. Mp: 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.42−7.33 (m, 3H), 7.23 (m, 1H), 7.10 (dd, 1H, J = 7.3, 1.8 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.91 (d, 1H, J = 8.2 Hz), 3.74 (s, 3H), 1.94 (m, 1H), 1.73−1.58 (m, 11H), 1.32−0.89 (m, 10H); ^{13}C NMR (75 MHz, THF-d_8) δ 157.6 (d, J_{CP} = 1.0 Hz), 148.3 (d, J_{CP} = 32.0 Hz), 136.5 (d, J_{CP} = 21.2 Hz), 133.0 (d, J_{CP} = 3.4 Hz), 133.0 (d, J_{CP} = 6.6 Hz), 132.6 (d, J_{CP} = 2.6 Hz), 131.3 (d, J_{CP} = 5.9 Hz), 129.1, 128.8 (d, J_{CP} = 1.2 Hz), 127.1, 120.2, 110.9, 55.3, 36.3 (d, J_{CP} = 16.2 Hz), 35.0 (d, J_{CP} = 15.9 Hz), 31.9 (d, J_{CP} = 18.3 Hz), 31.4 (d, J_{CP} = 18.0 Hz), 30.9 (d, J_{CP} = 12.8 Hz), 30.0 (d, J_{CP} = 6.9 Hz), 28.5−28.3 (4 resonances), 27.8, 27.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ −10.0; IR (neat, cm^{-1}) 2924, 2849, 1496, 1446, 1246, 749. Anal. Calcd for $C_{25}H_{33}OP$: C, 78.90; H, 8.76. Found: C, 78.62; H, 8.72.

2-Dicyclohexylphosphino-2′-hydroxybiphenyl (2a). A 50 mL Schlenk flask was charged sequentially with 2-dicyclohexylphosphino-2′-methoxybiphenyl (**1a**) (1.20 g, 3.15 mmol, 1 equiv) and dichloromethane (9.0 mL). The solution was cooled to −78 °C, and a solution of boron tribromide in dichloromethane (6.95 mL of a 1.0 M solution, 6.94 mmol, 2.2 equiv) was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 15 min, at which point the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 16 h, the mixture was quenched upon addition of saturated aqueous sodium bicarbonate solution (3 mL) and then transferred to a separatory funnel containing water (130 mL). The pH of the aqueous layer was adjusted to 7 with additional saturated aqueous sodium bicarbonate solution. The mixture was diluted with ethyl acetate (100 mL), and the layers were separated. The product was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were then washed with brine (4 × 100 mL) until the pH of the aqueous extract was ∼5. The organic layer was washed once more with brine (100 mL), dried over sodium sulfate, and concentrated in vacuo to afford the title compound (980 mg, 84%). Occasionally the product is contaminated with a boron complex (^{31}P NMR (121 MHz, $CDCl_3$) δ 34.4) and/or the phosphine oxide (^{31}P NMR (121 MHz, $CDCl_3$) δ 52.4). The former can be removed or converted to product by dissolving the solid in ethyl acetate and further washing with brine until the pH of the washes are neutral. The latter, if significant, can be removed by flash chromatography through a short plug of silica gel (5% EtOAc/hexanes). Mp: 131−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.44 (m, 2H), 7.33−7.26 (m, 2H), 7.10 (dd, 1H, J = 7.8, 1.8 Hz), 7.00−6.95 (m, 2H), 5.14 (br s, 1H), 2.07 (m, 1H), 1.77−1.50 (m, 11H), 1.34−0.83 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 145.1 (d, J_{CP} = 30.8 Hz), 135.0 (d, J_{CP} = 19.7 Hz), 133.0 (d, J_{CP} = 2.6 Hz), 131.8 (d, J_{CP} = 1.9 Hz), 131.6 (d, J_{CP} = 6.0 Hz), 130.0 (d, J_{CP} = 6.2 Hz), 129.4, 129.2, 127.6, 120.4, 116.5, 35.2 (d, J_{CP} = 14.7 Hz), 32.4 (d, J_{CP} = 10.9 Hz), 30.6 (d, J_{CP} = 14.5 Hz), 30.0−29.6 (2 resonances), 28.6, 27.7−27.1 (5 resonances), 26.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ −8.7; IR (neat, cm^{-1}) 3554, 3415 (br), 2924, 2849, 1446, 1182, 751. Anal. Calcd for $C_{24}H_{31}OP$: C, 78.64; H, 8.54. Found: C, 78.65; H, 8.45.

Resin-bound dicyclohexylphosphinobiphenyl 3a. A 25 mL Schlenk flask was charged with the Merrifield resin (608 mg of a 200−400 mesh resin containing 1.23 mmol/g Cl, 0.748 mmol, 1 equiv) and *N*,*N*-dimethylformamide (6.0 mL). The mixture was degassed and was allowed to swell for 60 min. Sodium hydride (50 mg of a 60% dispersion in mineral oil, 1.20 mmol, 1.6 equiv) was added to a 50 mL recovery flask containing a degassed solution of 2-dicyclohexylphosphino-2′-hydroxybiphenyl (**2a**) (370 mg, 1.01 mmol, 1.4 equiv) and DMF (4.5 mL); the reaction mixture was stirred at 25 °C for 15 min. The phosphine solution was then transferred via cannula to the Schlenk flask containing the resin. The recovery flask was rinsed with DMF (1.0 mL), which was also transferred to the reaction flask. The reaction mixture was degassed and was purged with argon. The flask was placed on an orbital shaker (400 rpm) at 25 °C for 23 h. The reaction mixture was transferred to a sintered glass funnel with DMF (2 × 5 mL). The resin was washed with the following (2 × 7 mL each): water, 1 N aqueous hydrochloric acid solution, water, methanol, dichloromethane, methanol, dichloromethane, and ether (3 × 7 mL). The tan resin **3a** was dried under vacuum to constant weight (817 mg, 96%, coupling efficiency of 85%).[22] When 100−200 mesh Merrifield resin was used, the average coupling efficiency was higher (91%). Gel phase ^{31}P NMR (121 MHz, C_6D_6) δ −10.6. Anal. Calcd for P (in duplicate): 2.33 (resin loading of 0.752 mmol/g phosphine).

General Procedure for Amination Reactions. A solution of $Pd(OAc)_2$ in toluene (1.00 mL of a 7.50 mM solution, 7.50 μmol, 1.00 mol %) was added to an oven-dried test tube (16 × 100 mm) containing resin **3a** (9.8 μmol, 1.3 mol %) and sealed with a septum. The mixture was stirred at 25 °C for 30−75 min. Sodium *tert*-butoxide (108 mg, 1.12 mmol, 1.50 equiv) was then added to the flask, and the system was purged with argon. Aryl halide (0.750 mmol, 1 equiv), amine (0.975 mmol, 1.30 equiv), and toluene (0.50 mL) were added sequentially via syringe. The flask was placed into an 80 °C oil bath, and the reaction mixture was stirred for 15−20 h. After cooling, the mixture was diluted with ether (5 mL), filtered through Celite, and rinsed with ether (2 × 5 mL). The combined organic layers were transferred to a separatory funnel and diluted with ether (50 mL). The organic layer was

washed with a saturated aqueous bicarbonate solution (3 × 50 mL), dried over sodium sulfate, and concentrated in vacuo to provide analytically pure product.

***N*-Methyl-*N*-(4-*tert*-butylphenyl)aniline** (Table 1, entries 1−2).[5] Entry 1: the reaction was performed using 1-*tert*-butyl-4-iodobenzene (135 μL), *N*-methylaniline (105 μL), and THF in place of toluene at 65 °C to provide the product as a tan oil (174 mg, 97%). Entry 2: the general procedure using 1-bromo-4-*tert*-butylbenzene (130 μL) and *N*-methylaniline (105 μL) afforded 172 mg (96%) of the title product.

***N*-Benzyl-2,5-dimethylaniline** (Table 1, entries 3−5).[5] Entry 3: the general procedure using 2-iodo-*p*-xylene (105 μL) and benzylamine (105 μL) gave 144 mg (91%) of the product as a yellow oil. Entry 4: the general procedure was modified by adding toluene (1.00 mL) to a test tube containing $Pd(OAc)_2$ (3.4 mg, 15 μmol, 2.0 mol %) and ligand **3a** (19 μmol, 2.5 mol %) for the catalyst premix. The remainder of the procedure using 2-bromo-*p*-xylene (105 μL) and benzylamine (105 μL) at 100 °C afforded 145 mg (92%) of the title compound. Entry 5: the general procedure using 2-chloro-*p*-xylene (101 μL) and benzylamine (105 μL) provided 151 mg (96%) of the product.

***N*-(3-Methoxyphenyl)-*n*-hexylamine** (Table 1, entry 6). The general procedure was performed using 3-iodoanisole (99 μL) and *n*-hexylamine (295 μL, 2.25 mmol, 3.00 equiv). The residue was purified by flash chromatography (2% EtOAc/hexanes) to afford the desired product as a pale yellow oil (130 mg, 84%) and the diarylation byproduct (8.2 mg, 3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, 1H, J = 8.1 Hz), 6.25 (m, 2H), 6.17 (t, 1H, J = 2.3 Hz), 3.79 (s, 3H), 3.64 (br s, 1H), 3.10 (t, 2H, J = 6.9 Hz), 1.63 (m, 2H), 1.44−1.31 (m, 6H), 0.92 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.0, 129.9, 106.0, 102.2, 98.6, 55.2, 44.1, 31.9, 29.7, 27.1, 22.9, 14.3; IR (neat, cm^{-1}) 3405, 2926, 2854, 1613, 1510, 1460, 1210, 1160, 1046, 826, 753. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.23. Found: C, 75.59; H, 10.25.

***N*-(4-*tert*-Butylphenyl)morpholine** (Table 1, entry 7).[5] The general procedure using 1-bromo-4-*tert*-butylbenzene (130 μL) and morpholine (85 μL) provided 146 mg (89%) of the title compound as an ivory solid.

***N*,*N*-Dibutyl-3,5-dimethylaniline** (Table 1, entry 8). The general procedure using 5-bromo-*m*-xylene (102 μL) and dibutylamine (165 μL) gave 139 mg (79%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.29 (s, 2H), 3.25 (t, 4H, J = 7.6 Hz), 2.28 (s, 6H), 1.57 (m, 4H), 1.36 (m, 4H), 0.97 (t, 6H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 138.7, 117.3, 109.8, 51.0, 29.8, 22.2, 20.7, 14.3; IR (neat, cm^{-1}) 2957, 2867, 1599, 1485, 1366, 1194, 814. Anal. Calcd for $C_{16}H_{27}N$: C, 82.33; H, 11.68. Found: C, 82.07; H, 11.49.

***N*-(4-Methoxyphenyl)morpholine** (Table 1, entry 9).[30] The general procedure using 4-bromoanisole (94 μL) and morpholine (85 μL) afforded the title compound as a tan solid (125 mg, 86%).

***N*-(2,5-Dimethylphenyl)-*m*-toluidine** (Table 1, entries 10−11). Entry 10: the general procedure was modified by adding toluene (1.00 mL) to a test tube containing $Pd_2(dba)_3$ (3.4 mg, 3.8 μmol, 0.50 mol %) and ligand **3a** (9.8 μmol, 1.3 mol %). The remainder of the procedure using 2-bromo-*p*-xylene (105 μL) and *m*-toluidine (105 μL) at 100 °C provided the product as a tan oil (157 mg, 99%). Entry 11: the general procedure was modified by adding toluene (1.00 mL) to a test tube containing $Pd_2(dba)_3$ (5.2 mg, 5.6 μmol, 0.75 mol %) and ligand **3a** (14 μmol, 1.9 mol %). The remainder of the procedure using 2-chloro-*p*-xylene (101 μL) and *m*-toluidine (105 μL) at 100 °C gave the title compound in 98% (156 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.08 (m, 3H), 6.80−6.73 (m, 4H), 5.32 (br s, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 141.1, 139.2, 136.5, 130.8, 129.2, 125.3, 122.8, 121.3, 119.7, 118.2, 114.6, 21.8, 21.4, 17.7; IR (neat, cm^{-1}) 3388, 2920, 1604, 1577, 1476, 1310, 1170, 1000, 771. Anal. Calcd for $C_{15}H_{17}N$: C, 85.25; H, 8.13. Found: C, 85.28; H, 8.30.

(30) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

***N*-Methyl-*N*-phenyl-*p*-toluidine** (Table 1, entry 12).[30] The reaction was performed using 4-chlorotoluene (89 μL), *N*-methylaniline (105 μL), and THF in place of toluene at 65 °C to provide the product as a tan oil (131 mg, 89%).

***N*-(4-Methylphenyl)morpholine** (Table 1, entry 13).[30] The general procedure using 4-chlorotoluene (89 μL) and morpholine (85 μL) afforded the title compound as a yellow solid (122 mg, 92%).

General Procedure for Suzuki Reactions. THF (1.00 mL) was added to an oven-dried test tube (16 × 100 mm) sealed with a septum containing resin **3a** (5.2 μmol, 0.70 mol %) and $Pd_2(dba)_3$ (1.7 mg, 1.9 μmol, 0.25 mol %). The mixture was stirred at 25 °C for 30−75 min. Aryl halide (0.750 mmol, 1 equiv) was added via syringe. Cesium carbonate (489 mg, 1.50 mmol, 2.00 equiv) and boronic acid (0.900 mmol, 1.20 equiv) were added simultaneously to the flask, and the system was purged with argon. THF (0.50 mL) was added via syringe. The flask was placed into a 65 °C oil bath, and the reaction mixture was stirred for 17−21 h. After cooling, the mixture was diluted with ether (5 mL), filtered through Celite, and rinsed with ether (2 × 5 mL). The combined organic layers were transferred to a separatory funnel and diluted with ether (50 mL). The organic layer was washed with a 1 N aqueous sodium hydroxide solution (3 × 50 mL), dried over sodium sulfate, and concentrated in vacuo to provide analytically pure product.

3-Methoxy-4′-methylbiphenyl (Table 2, entry 1). The general procedure was modified by adding a solution of $Pd_2(dba)_3$ in THF (1.0 mL of a 0.75 mM solution, 0.75 μmol, 0.10 mol %) to a test tube containing ligand **3a** (2.2 μmol, 0.30 mol %). The remainder of the procedure using 3-iodoanisole (99 μL) and *p*-tolylboronic acid (122 mg) provided the title compound as a yellow oil (138 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 2H, J = 8.0 Hz), 7.36 (t, 1H, J = 7.8 Hz), 7.26 (d, 2H, J = 7.7 Hz), 7.18 (d, 1H, J = 7.7 Hz), 7.13 (t, 1H, J = 2.1 Hz), 6.89 (dd, 1H, J = 8.2, 2.5 Hz), 3.88 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 142.7, 138.2, 137.2, 129.8, 129.5, 127.1, 119.6, 112.8, 112.4, 55.4, 21.4; IR (neat, cm^{-1}) 3025, 2938, 1601, 1481, 1296, 1220, 1175, 1053, 1032, 867, 818, 777. Anal. Calcd for $C_{14}H_{14}O$: C, 84.80; H, 7.13. Found: C, 84.57; H, 7.18.

4-*tert*-Butyl-2′-methylbiphenyl (Table 2, entry 2).[4] The general procedure was modified by adding a solution of $Pd_2(dba)_3$ in THF (1.5 mL of a 0.75 mM solution, 1.1 μmol, 0.15 mol %) to a test tube containing ligand **3a** (3.4 μmol, 0.45 mol %). The remainder of the procedure using 1-*tert*-butyl-4-iodobenzene (135 μL), *o*-tolylboronic acid (122 mg), and no additional THF gave the title compound as a yellow oil (164 mg, 98%).

4-*tert*-Butylbiphenyl (Table 2, entry 3).[4] The general procedure using 1-bromo-4-*tert*-butylbenzene (130 μL) and phenylboronic acid (110 mg) afforded the title compound as a yellow solid (155 mg, 98%).

2,6-Dimethylbiphenyl (Table 2, entry 4).[4] The general procedure using 2-bromo-*m*-xylene (100 μL) and phenylboronic acid (110 mg) provided the title compound as a pale yellow oil (124 mg, 91%).

2,5-Dimethyl-2′-methylbiphenyl (Table 2, entries 5 and 8).[4] Entry 5: the general procedure using 2-bromo-*p*-xylene (105 μL) and *o*-tolylboronic acid (153 mg, 1.12 mmol, 1.50 equiv) gave the product as a yellow oil (146 mg, 99%). Entry 8: the general procedure using 2-chloro-*p*-xylene (101 μL), *o*-tolylboronic acid (306 mg, 2.25 mmol, 3.00 equiv), $Pd_2(dba)_3$ (3.4 mg, 3.8 μmol, 0.50 mol %), and ligand **3a** (9.75 μmol, 1.30 mol %) provided the title compound (146 mg, 99%).

3-(1,3-Dioxolane)-2′-methoxybiphenyl (Table 2, entry 6).[4] The general procedure using 2-(3-bromophenyl)-1,3-dioxolane (115 μL), 2-methoxyphenylboronic acid (137 mg), $Pd_2(dba)_3$ (2.4 mg, 2.6 μmol, 0.35 mol %), and ligand **3a** (7.50 μmol, 1.00 mol %) afforded the product as a viscous oil (175 mg, 91%).

3-Carbomethoxy-4′-methylbiphenyl (Table 2, entry 7). The general procedure using methyl 3-chlorobenzoate (105 μL) and *p*-tolylboronic acid (152 mg, 1.12 mmol, 1.50 equiv) provided the product as a yellow oil (154 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (t, 1H, J = 1.7 Hz), 8.00 (dt, 1H, J =

7.7, 1.7 Hz), 7.78 (ddd, 1H, J = 7.7, 1.9, 1.2 Hz), 7.55−7.48 (m, 3H), 7.28 (d, 2H, J = 6.6 Hz), 3.96 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 141.4, 137.6, 137.2, 131.3, 130.6, 129.7, 128.8, 128.1, 128.0, 127.0, 52.3, 21.3; IR (neat, cm^{-1}) 3016, 2950, 1724, 1440, 1307, 1246, 1111, 811, 756. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.61; H, 6.25. Found: C, 79.85; H, 6.36.

2,5-Dimethyl-2′-methoxybiphenyl (Table 2, entry 9). The general procedure using 2-chloro-*p*-xylene (101 μL), 2-methoxyphenylboronic acid (342 mg, 2.25 mmol, 3.00 equiv), $Pd_2(dba)_3$ (3.4 mg, 3.8 μmol, 0.50 mol %), and ligand **3a** (9.75 μmol, 1.30 mol %) afforded the product as a tan oil (144 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (ddd, 1H, J = 8.2, 7.4, 1.9 Hz), 7.15 (dd, 2H, J = 7.3, 1.8 Hz), 7.08 (d, 1H, J = 7.8 Hz), 7.04−6.95 (m, 3H), 3.78 (s, 3H), 2.36 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 138.5, 134.8, 133.8, 131.1, 131.0, 130.7, 129.5, 128.6, 128.2, 120.5, 110.6, 55.5, 21.2, 19.7; IR (neat, cm^{-1}) 3000, 2922, 1595, 1579, 1488, 1457, 1431, 1236, 1114, 1026, 751. Anal. Calcd for $C_{15}H_{16}O$: C, 84.85; H, 7.61. Found: C, 84.76; H, 7.67.

General Recycling Procedures. Reactions were performed as above except on a 1.00 mmol scale (0.500 M solution) and in a 10 mL side arm flask fitted with an 18 mm diameter sintered glass filter disk. After cooling, the mixture was diluted with ether (10 mL) and filtered through the side arm with a positive argon pressure. The resin was further washed with ether (2 × 7 mL) and filtered, and the combined organic washes were subjected to the workup procedures described above for product isolation. The resin was rinsed with water (2 × 7 mL), *tert*-butyl alcohol (2 × 7 mL), and ether (3 × 7 mL) and was dried in vacuo in the reaction flask for at least 3 h. Subsequent reactions were initiated by adding solvent (1.50 mL) via syringe to the reaction flask containing the used resin. The mixture was stirred at 25 °C for 30−75 min. The rest of the experiment was set up as stated in the previous procedures after the premixing protocol.

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