Ion-Tagged Phosphines as Ligands for Suzuki Coupling of Aryl Halides in a Phosphonium Ionic Liquid

Adam J. Keith,[a] Stephen D. Kosik,[b] L. M. Viranga Tillekeratne,[b] Mark R. Mason*[a]

[a] Department of Chemistry and School of Green Chemistry and Engineering, The University of Toledo, Toledo, OH 43606, USA
Fax +1(419)5304033; E-mail: mmason5@utoledo.edu

[b] Department of Medicinal and Biological Chemistry and School of Green Chemistry and Engineering, The University of Toledo, Toledo, OH 43606, USA

Received: 31.12.2013; Accepted after revision: 28.01.2014

Abstract: Gramine-based N-substituted phosphines were synthesized and utilized as ligands in Suzuki–Miyaura coupling of aryl bromides and chlorides in the room temperature ionic liquid trihexyltetradecylphosphonium bis(trifluoromethanesulfonyl)imide. Increased yields were achieved with ion-tagged ligands compared to ligands bearing pendant amines, likely due to higher solubility of the former. Cyclohexyl groups on the phosphine moiety generally resulted in higher yields than *tert*-butyl groups. In addition, a biphasic ionic liquid/water system outperformed catalysis in neat ionic liquid and provided higher yields at lower temperatures.

Key words: palladium, catalysis, ionic liquids, cross-coupling, green chemistry

Biaryls are commonly utilized motifs in the synthesis of biologically active compounds, including pharmaceuticals and herbicides.[1,2] They are commonly prepared by metal-catalyzed sp^2–sp^2 carbon–carbon bond-formation reactions of aryl halides, a widely used method of which is the Suzuki–Miyaura (SM) coupling reaction between aryl halides and aryl boronic acids.[3,4] In view of the vast potential of this reaction in the synthesis of commercially important compounds, efforts are being made to modify the reaction conditions to make it more amenable to 'greener' solvents and milder reaction conditions. Besides, the reaction is slow when aryl chlorides, especially those with deactivating electron-donating substituents, are used. Therefore, new catalysts that improve the efficiency of the reaction with less reactive and more commonly available aryl chlorides as substrates are being sought.

Ligation of palladium by phosphorus donors is the most commonly employed strategy for increasing catalytic activity in SM reactions. The biaryl phosphine ligands reported by Buchwald and co-workers are highly successful, even for the coupling of chloroarenes.[5] Ligands developed by Beller and co-workers, which feature a dialkyl phosphine moiety bonded to the C2 position of indole, are also commonly used and commercially available.[6] The Mason group has previously reported the synthesis of *N*-indolyl[7] and gramine-substituted phosphines,[8] similar to the Beller ligands. Kwong and co-workers[9] subsequently reported the use of *N*-indolyl phosphines for Suzuki–Miyaura cross-coupling reactions. The major drawback of these phosphine ligand sets is the difficulty in recovering the palladium catalyst and the high catalyst loading.

The high cost of palladium and increasingly stringent environmental regulations warrant innovations which recycle the catalyst, reduce metal leaching, or minimize catalyst loading. A commonly employed strategy to address catalyst recyclability and leaching is application of ionic liquids (ILs) as reaction media.[10] The active catalytic species in IL is believed to be mononuclear palladium(0), but upon heating the palladium aggregates, leading to formation of inactive palladium black.[11] It has been proposed by Dyson and co-workers[12] that some ILs act as nanoparticle stabilizers and reduce palladium black clustering. Palladium nanoparticles[13] are believed to act as reservoirs for mononuclear metal species, allowing for increased catalytic activity. Recycling of active catalyst in IL may be achieved by developing a catalyst with high affinity for the ionic liquid and using an immiscible solvent to extract products and unreacted starting materials. Although there are a number of examples of Suzuki–Miyaura coupling reactions in ionic liquids, only a few use phosphonium-based ILs.[14] Even though phosphonium-based ILs are miscible with a broad spectrum of organic solvents, a system can be envisioned where extraction is conducted using supercritical CO_2.[15–20] Such a system would also have the added advantage of eliminating the undesirable effects resulting from use of organic solvents.

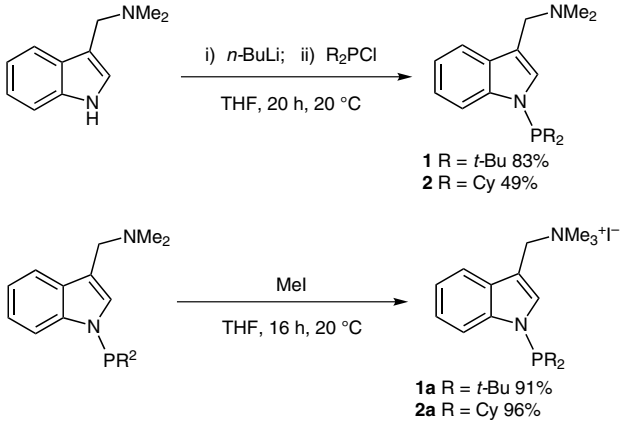
Herein we report the use of room temperature ionic liquid trihexyltetradecylphosphonium bis(trifluoromethylsulfonyl)imide ($[P_{66614}][NTf_2]$) as reaction medium for palladium-catalyzed Suzuki–Miyaura coupling of phenylboronic acid and aryl halides using a new class of indole-based phosphine ligands. The synthesis of *N*-dialkylphosphinogramine ligands and their grammonium salts is also described. The addition of pendant amino and, especially, ammonium moieties to indole enhances ligand and catalyst solubility in ionic liquids and may allow catalyst recycling. Use of ion-tagged phosphines for improvement of solubility in polar solvents and ILs is well documented.[21–24]

Sterically demanding[25] and electron-rich[26,27] phosphines constitute the most active and widely employed ligands in

SYNLETT 2014, 25, 0977–0982
Advanced online publication: 14.03.2014
DOI: 10.1055/s-0033-1340846; Art ID: ST-2013-S1178-L

Suzuki–Miyaura reactions. However, sensitivity to oxygen and high cost are drawbacks that limit their general applicability. *N*-Dialkylphosphinogramines (**1**, **2**) are attractive as ligands because they are easily prepared from inexpensive materials and exhibit robust stability compared to many alkyl phosphines. Methylation of the pendant amine to produce the corresponding ammonium salts (**1a**, **2a**) is an efficient and inexpensive method of increasing the solubility of these compounds in ionic liquids.

Phosphines **1** and **2** were synthesized by the reaction of deprotonated gramine with *t*-Bu_2PCl and Cy_2PCl, respectively (Scheme 1). Subsequent methylation with iodomethane afforded the ion-tagged phosphines **1a** and **2a**.



Scheme 1

The new phosphines were characterized by NMR (^1H, ^{13}C, ^{31}P) spectroscopy, mass spectrometry (ESI), and elemental analysis. The molecular structure of **1a** was further confirmed by X-ray crystallography (Figure 1). Characterization details are provided in the experimental section and representative spectra are available in the supporting information.

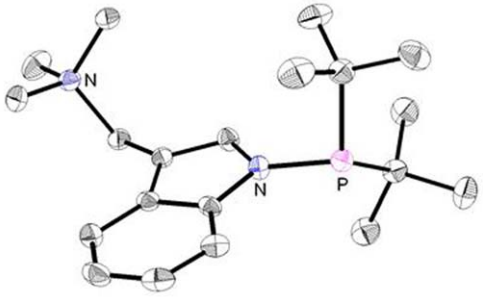
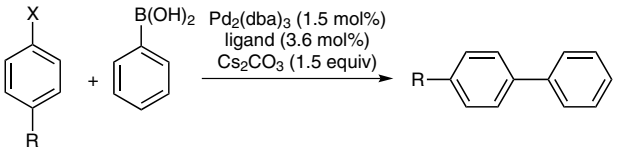


Figure 1 ORTEP diagram of **1a** cation. Hydrogen atoms and iodide ion omitted for clarity.

Initial catalyst screening was conducted using 4-chlorotoluene with dimethylformamide (DMF) as the solvent. As expected, higher yields were obtained for the non-methylated ligands (**1** and **2**) due to their higher solubility in DMF (results not shown). No product was obtained in the absence of phosphine ligands, thus confirming that these ligands improve the efficiency of the dipalladium dibenzylideneacetone catalyst.

Catalyst screening was then conducted in trihexyltetradecylphosphonium bis(trifluoromethylsulfonyl)imide ($[P_{66614}][NTf_2]$) IL as solvent (Table 1). Higher yields were observed with the ligands carrying pendant ionic ammonium groups (**1a** and **2a**) compared to the non-ionic ligands. This could be attributed to the higher solubility of the ionic phosphine ligands in the ionic liquid. Solubility tests indicated an approximately five-fold increase in the solubility of ligands in IL upon conversion to the ammonium salt. In general the yields obtained with non-ionic ligands in IL were comparable to yields obtained in DMF under similar conditions.

Table 1 Suzuki Coupling of 4-Arylhalides and Phenylboronic Acid in $[P_{66614}][NTf_2]$ at 180 °C[a]



Entry	R	X	Ligand	Yield (%)[b] Thermal	MW
1	Me	Cl	**1**	15	13
2	Me	Cl	**1a**	34	15
3	Me	Cl	**2**	20	13
4	Me	Cl	**2a**	32	20
5	Me	Cl	none	0	0
6	CF_3	Cl	**1**	25	31
7	CF_3	Cl	**1a**	33	23
8	CF_3	Cl	**2**	48	58
9	CF_3	Cl	**2a**	61	60
10	CF_3	Cl	none	13	12
11	Me	Br	**1**	49	26
12	Me	Br	**1a**	45	28
13	Me	Br	**2**	34	29
14	Me	Br	**2a**	54	45
15	Me	Br	none	14	14
16	CF_3	Br	**1**	49	39
17	CF_3	Br	**1a**	58	47
18	CF_3	Br	**2**	46	55
19	CF_3	Br	**2a**	64	58
20	CF_3	Br	none	41	41

[a] Reaction time: 48 h, thermal; 3 h, microwave (MW).
[b] GC yields.

The rate-limiting step of Suzuki–Miyaura reaction is the oxidative addition of the aryl halide to palladium(0). Electron-withdrawing substituents on the aryl ring therefore activate the aryl halide to oxidative addition. As expected, switching the substituent from methyl to trifluoromethyl resulted in a significant increase in the reaction yields (Table 1, entries 6–10). Interestingly, better yields were obtained with ligands carrying less bulky dicyclohexylphosphino compared to those with di-*tert*-butylphosphino groups. This is likely due to higher accessibility of metal site when the phosphine is smaller in size.

With aryl chlorides with trifluoromethyl activating group, some conversion was observed in the absence of ligands albeit in significantly lower quantities (Table 1, entry 10). For deactivating methyl substituents, higher yields were obtained with more reactive aryl bromides (Table 1, entries 11–15). The substituent effects too were as predicted with aryl chlorides, with methyl resulting in much lower yields than trifluoromethyl. However, the substituent effect is less pronounced with aryl bromides, underscoring the need for effective catalytic systems for unactivated aryl halides in Suzuki–Miyaura reaction. As was observed for aryl chlorides with activating trifluoromethyl groups, little product formation was observed in the absence of ligand with aryl bromides with deactivating methyl group (Table 1, entry 15).

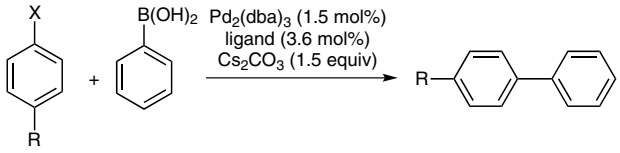
Highest yields were observed with 4-bromobenzotrifluoride, the most active of the substrates tested. In fact, trials conducted in the absence of ligand saw a significant increase in yield (Table 1, entry 20).

Although the yields were better when a phosphine ligand was added, the differences were not as significant as with the less active substrates. This large increase in yield in the absence of a phosphine ligand is likely due to 4-bromobenzotrifluoride being reactive enough that nanoparticles are rate competitive with the phosphine complex.

Microwave heating has become a common method to decrease reaction times in organic syntheses and, in particular, Suzuki–Miyaura cross-coupling reactions.[28] A general trend across Table 1 is that traditional thermal heating produced better yields than the microwave heating. Nevertheless, microwave conversion takes less time and is much more energy efficient.

Welton,[29] Dyson,[12a] and others have reported that adding water or alcohols to SM cross-coupling reactions in ILs increases product yields, presumably due to increased solubility of the base. Our catalytic trials with non-ionic amine ligands in neat ionic liquid always contained some undissolved base. To test the effect of water, a second set of screenings was conducted using an ionic liquid/water mixture as solvent (Table 2). The results were very pronounced. Not only the yields were increased, but the reactions became more reproducible. In neat ionic liquid there was often noticeable palladium black formation and the reaction mixture after heating ranged in color from yellow to violet. When water was added there was little to no precipitate of palladium black following heating and the ionic liquid phase was reproducibly yellow in color. A variable temperature study showed no significant reduction in product when the reaction temperature was lowered from 180 °C to 160 °C in the binary mixture for 4-chlorotoluene. However, decreasing the temperature further resulted in lower yields.

Table 2 Suzuki Coupling of 4-Arylhalides and Phenylboronic Acid in $[P_{66614}][NTf_2]$ and Water at 160 °C[a]



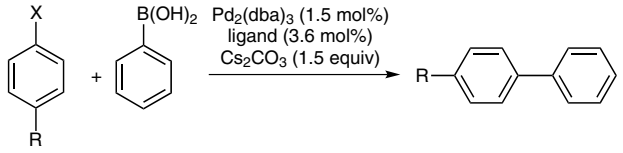
Entry	R	X	Ligand	Yield (%)[b]	
				Thermal	MW
1	Me	Cl	**1**	19	17
2	Me	Cl	**1a**	40	45
3	Me	Cl	**2**	39	25
4	Me	Cl	**2a**	49	54
5	CF_3	Cl	**1**	62	56
6	CF_3	Cl	**1a**	77	79
7	CF_3	Cl	**2**	68	67
8	CF_3	Cl	**2a**	83	85
9	Me	Br	**1**	64	57
10	Me	Br	**1a**	87	82
11	Me	Br	**2**	90	90
12	Me	Br	**2a**	96	91
13	CF_3	Br	**1**	48	46
14	CF_3	Br	**1a**	98	99
15	CF_3	Br	**2**	83	74
16	CF_3	Br	**2a**	99	99

[a] Reaction time: 48 h, thermal; 3 h, microwave (MW).
[b] GC yields.

The results of Table 2 mimic those of Table 1 with similar trends observed based on the activity of the aryl halide, but with improved yields and lower standard deviations between replicated runs. In particular the yields with aryl chlorides were much improved. For many of the catalytic trials with aryl bromides the reactions gave almost quantitative yields (Table 2, entries 12, 14 and 16). In order to further alleviate the harsh temperatures used, a set of catalytic trials was conducted at 120 °C (Table 3). The yields obtained were comparable to those obtained at 160 °C, and in some instances were even better (Table 3, entries 1,

3, and 4), probably due to decomposition of product at higher temperatures.

Table 3 Suzuki Coupling of 4-Arylbromides and Phenylboronic Acid in $[P_{66614}][NTf_2]$ and Water at 120 °C



Entry	R	X	Ligand	Yield (%)[b] Thermal	MW
1	Me	Br	**1**	79	80
2	Me	Br	**1a**	78	69
3	Me	Br	**2**	97	97
4	Me	Br	**2a**	98	98
5	CF_3	Br	**1**	52	50
6	CF_3	Br	**1a**	99	99
7	CF_3	Br	**2**	82	78
8	CF_3	Br	**2a**	99	97

[a] Reaction time: 48 h, thermal; 3 h, microwave (MW).
[b] GC yields.

In conclusion, two dialkylphosphinogramines (**1**, **2**) and their ion-tagged derivatives (**1a**, **2a**) have been prepared and fully characterized.[30] These phosphines are effective as ligands for Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid in a phosphonium IL with either traditional or microwave heating. The ion-tagged derivatives exhibit dramatically increased solubility in the IL and increased product yield compared with those for the neutral ligands **1** and **2**. Interestingly, ligands with dicyclohexylphosphino groups were found to give higher yields compared to ligands with more sterically demanding di-*tert*-butylphosphino substituents. Addition of water to the IL also led to a dramatic increase in yields at lower temperature. Although promising and easily synthesized, the catalyst systems reported here do not function under the milder conditions achievable using the Buchwald,[5] Beller,[6] or Kwong[9] ligands in traditional organic solvents or ion-tagged phosphines reported to function under mild conditions in $[bmpy][NTf_2]/H_2O$.[22,23] Derivatives of ligands **1** and **2** do provide opportunity for further optimization as recyclable catalysts in the SM reaction. In this context, SM coupling reactions with electron-rich C2-substituted dialkylphosphinogramines are in progress and those results will be reported elsewhere.

Acknowledgment

Partial funding of this research was provided by the Interdisciplinary Research Initiation program at The University of Toledo. The authors thank Cytec for providing tetradecyltrihexylphosphonium chloride free of charge. We thank Professor Jared Anderson and his group members for suggestions on the preparation, purification, and handling of ionic liquids, and Dr. Kristin Kirschbaum and Chris Gianopoulos for advice on the crystallographic refinement and solution for **1a**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Yasuda, N. *J. Organomet. Chem.* **2002**, *653*, 279.
(2) Indolese, A. F.; Schnyder, A. *Curr. Sci.* **2000**, *78*, 1336.
(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *Chem. Commun.* **2005**, 4759.
(4) (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Dembitsky, V. M.; Abu, A. H.; Srebnik, M. *Stud. Inorg. Chem.* **2005**, *22*, 119.
(5) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(6) (a) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983. (b) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38.
(7) (a) Barnard, T. S.; Mason, M. R. *Organometallics* **2001**, *20*, 206. (b) Barnard, T. S.; Mason, M. R. *Inorg. Chem.* **2001**, *40*, 5001.
(8) Mason, M. R.; Beckford, F. A.; Kirschbaum, K.; Gorecki, B. J. *Inorg. Chem. Commun.* **2005**, *8*, 331.
(9) So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 2795.
(10) (a) Ni, B.; Headley, A. D. *Chem. Eur. J.* **2010**, *16*, 4426. (b) Li, L.; Wang, J.; Wu, T.; Wang, R. *Chem. Eur. J.* **2012**, *18*, 7842.
(11) (a) Reetz, M.; de Vries, J. G. *Chem. Commun.* **2004**, 1559. (b) Alimardanov, A.; Schmieder-van de Vondervoort, L.; de Vries, A. H. M.; de Vries, J. G. *Adv. Synth. Catal.* **2004**, *346*, 1812. (c) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (d) Huang, W.; Guo, J.; Xiao, Y.; Zhu, M.; Zou, G.; Tang, J. *Tetrahedron* **2005**, *61*, 9783. (e) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2006**, *47*, 197.
(12) (a) Yan, N.; Yang, X.; Fei, Z.; Li, Y.; Kou, Y.; Dyson, P. J. *Organometallics* **2009**, *28*, 937. (b) Yang, X.; Fei, Z.; Zhao, D.; Ang, W. H.; Li, Y.; Dyson, P. J. *Inorg. Chem.* **2008**, *47*, 3292. (c) Fei, Z.; Geldbach, T. J.; Zhao, D.; Dyson, P. J. *Chem. Eur. J.* **2006**, *12*, 2122. (d) Chiappe, C.; Pieraccini, D.; Zhao, D.; Fei, Z.; Dyson, P. J. *Adv. Synth. Catal.* **2006**, *348*, 68. (e) Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876.
(13) Yu, Y.; Hu, T.; Chen, X.; Xu, K.; Zhang, J.; Huang, J. *Chem. Commun.* **2011**, *47*, 3592.
(14) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. *Chem. Commun.* **2002**, 1986.
(15) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
(16) Welton, T. *Green Chem.* **2008**, *10*, 483.
(17) Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature (London)* **1999**, *399*, 28.
(18) Blanchard, L. A.; Brennecke, J. F. *Ind. Eng. Chem. Res.* **2001**, *40*, 287.
(19) Blanchard, L. A.; Gu, Z.; Brennecke, J. F. *J. Phys. Chem. B* **2001**, *105*, 2437.
(20) Hintermair, U.; Gong, Z.; Serbanovic, A.; Muldoon, M. J.; Santini, C. C.; Cole-Hamilton, D. J. *Dalton Trans.* **2010**, *39*, 8501.
(21) Sebesta, R.; Kmentova, I.; Toma, S. *Green Chem.* **2008**, *10*, 484.

(22) Lombardo, M.; Chiarucci, M.; Trombini, C. *Green Chem.* **2009**, *11*, 574.
(23) Papagni, A.; Trombini, C.; Lombardo, M.; Bergantin, S.; Chams, A.; Chiarucci, M.; Miozzo, L.; Parravicini, M. *Organometallics* **2011**, *30*, 4325.
(24) Tindale, J. J.; Ragogna, P. J. *Can. J. Chem.* **2010**, *88*, 27.
(25) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(26) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787.
(27) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104.
(28) Bedford, R. B.; Butts, C. P.; Hurst, T. E.; Lidstrom, P. *Adv. Synth. Catal.* **2004**, *346*, 1627.
(29) McLachlan, F.; Mathews, C. J.; Smith, P. J.; Welton, T. *Organometallics* **2003**, *22*, 5350.
(30) **Synthesis of 1-(Di-*tert*-butylphosphino)-3-dimethylaminomethylindole (1)**: A solution of *n*-butyllithium (1.6 M, 7.2 mL, 11.5 mmol) in hexanes was added via syringe to a cooled (–78 °C) solution of gramine (2.01 g, 11.5 mmol) in THF (50 mL). The resulting yellow solution was stirred for 1 h at r.t. before again cooling to –78 °C. A solution of *t*-Bu_2PCl (2.083 g, 11.53 mmol) in THF (5 mL) was added via cannula. The reaction solution was stirred for 20 h at ambient temperature, after which the volatiles were removed in vacuo. The waxy yellow solid was dissolved in CH_2Cl_2 and the precipitated solids were removed by filtration over a pad of Celite on a sintered glass funnel. CH_2Cl_2 was removed in vacuo. Colorless crystals of 1-(di-*tert*-butylphosphino)-3-dimethylaminomethylindole (2.93 g, 83%) were grown from the slow evaporation of MeCN at r.t.; mp 80 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H7), 7.65 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H4), 7.35 (s, 1 H, H2), 7.21 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H6), 7.14 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H5), 3.64 (s, 2 H, CH_2), 2.28 (s, 6 H, NMe_2), 1.22 (d, $^3J_{HP}$ = 13.2 Hz, 18 H, CMe_3). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 144.5 (s, C4a), 129.9 (d, $^2J_{CP}$ = 8.9 Hz, C2), 129.0 (d, C7a), 122.1 (d, C6), 120.1 (s, C5), 119.0 (s, C4), 116.1 (s, C3), 113.2 (d, $^3J_{CP}$ = 20.2 Hz, C7), 55.0 (s, CH_2), 45.6 (s, NMe_2), 35.3 (d, $^1J_{CP}$ = 25.0 Hz, PC), 29.4 (d, $^2J_{CP}$ = 16.4 Hz, PC*Me*$_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 71.3 (s). MS (ESI): *m/z* (%) = 341.1 (5) $[MNa]^+$, 318.6 (18) $[MH]^+$, 274.2 (100) $[M – NMe_2]^+$. Anal. Calcd for $C_{19}H_{31}N_2P$: C, 71.66; H, 9.81; N, 8.80. Found: C, 71.70; H, 10.39; N, 8.83.

Synthesis of 1-(Di-*tert*-butylphosphino)-3-trimethylammoniummethylindole Iodide (1a): Iodomethane (0.391 g, 2.75 mmol) was added to a solution of compound **1** (0.844 g, 2.75 mmol) in toluene (60 mL) via syringe. The reaction mixture was stirred for 16 h at ambient temperature after which the white powder was isolated via filtration. 1-(Di-*tert*-butylphosphino)-3-trimethylammoniummethylindole iodide (1.15 g, 91%) was obtained by washing the solids with hexanes (10 mL) and drying in vacuo; mp 224 °C (dec.). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.03 (s, 1 H, H2), 7.83 (m, 2 H, H4, H7), 7.27 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H5), 7.22 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H6), 4.78 (s, 2 H, CH_2), 3.08 (s, 9 H, NMe_3), 1.18 (d, $^3J_{HP}$ = 12.8 Hz, 18 H, CMe_3). ^{13}C NMR (150.8 MHz, DMSO-d_6): δ = 143.5 (d, $^2J_{CP}$ = 20.51 Hz, C7a), 136.3 (s, C2), 128.2 (d, C4a), 122.7 (s, C5), 121.1 (s, C6), 118.9 (s, C7), 113.1 (s, C4), 106.3 (s, C3), 60.1 (s, CH_2), 51.7 (s, NMe_3), 34.7 (d, $^1J_{CP}$ = 25.49 Hz, PC), 28.7 (d, $^2J_{CP}$ = 15.99 Hz, PC*Me*$_3$). ^{31}P NMR (161.9 MHz, DMSO-d_6): δ = 75.0 (s). MS (ESI): *m/z* (%) = 274.1 (100) $[M – NMe_3]^+$. Anal. Calcd for $C_{20}H_{34}N_2PI$: C, 52.18; H, 7.44; N, 6.08. Found: C, 52.26; H, 7.77; N, 6.06.

Synthesis of 1-(Dicyclohexylphosphino)-3-dimethylaminomethylindole (2): A solution of *n*-butyllithium (1.6 M, 3.7 mL, 5.9 mmol) in hexanes was added via syringe to a cooled (–78 °C) solution of gramine (1.01 g, 5.8 mmol) in THF (25 mL). The resulting yellow solution was stirred for 1 h at r.t. before cooling again to –78 °C. A solution of Cy_2PCl (1.35 g, 5.8 mmol) in THF (5 mL) was added via cannula. The reaction solution was stirred for 20 h at ambient temperature, after which the volatiles were removed in vacuo. The waxy yellow solid was dissolved in CH_2Cl_2, the insoluble solids were removed by filtration over a pad of Celite on a sintered glass funnel, and CH_2Cl_2 was removed in vacuo. Colorless crystals of 1-(dicyclohexylphosphino)-3-dimethylaminomethyl indole (1.05 g, 49%) were grown from the slow evaporation of MeCN at r.t.; mp 71 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H7), 7.62 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H4), 7.20 (t, $^3J_{HH}$ = 6.6 Hz, 1 H, H6), 7.14 (s, 1 H, H2), 7.12 (t, $^3J_{HH}$ = 8.4 Hz, 1 H, H5), 3.63 (s, 2 H, CH_2), 2.28 (s, 6 H, NMe_2), 2.09 (br s, 2 H, Cy), 1.85 (d, *J* = 10.8 Hz, 2 H, Cy), 1.76 (d, *J* = 13.2 Hz, 2 H, Cy), 1.65 (m, 4 H, Cy), 1.47 (br s, 2 H, Cy), 1.31 (m, 2 H, Cy), 1.14 (m, 8 H, Cy). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 143.4 (br s, C4a), 129.7 (br s, C2), 127.9 (br s, C7a), 122.1 (s, C6), 120.1 (br s, C5), 119.2 (s, C4), 116.3 (s, C3) 112.7 (d, $^3J_{CP}$ =16.0 Hz, C7), 54.9 (s, CH_2), 45.6 (s, NMe_2), 36.5 (d, $^2J_{CP}$ = 14.5 Hz, PCH*C*H$_2$), 29.5 (d, $^1J_{CP}$ = 20.5 Hz, PCH), 28.2 (d, $^3J_{CP}$ = 6.7 Hz, PCHCH$_2$*C*H$_2$), 26.9 (d, $^2J_{CP}$ = 13.8 Hz, PCH*C*H$_2$), 26.8 (d, $^3J_{CP}$ = 7.6 Hz, PCHCH$_2$*C*H$_2$), 26.4 (s, PCHCH$_2$CH$_2$*C*H$_2$). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 48.7 (s). MS (ESI): *m/z* (%) = 393.6 (34) $[MNa]^+$, 371.5 (5) $[MH]^+$, 326.6 (100) $[M – NMe_2]^+$. Anal. Calcd for $C_{23}H_{35}N_2P$: C, 74.56; H, 9.52; N, 7.56. Found: C, 74.90; H, 9.82; N, 7.38.

Synthesis of 1-(Dicyclohexylphosphino)-3-trimethylammonium-methylindole Iodide (2a): Iodomethane (0.193 g, 1.36 mmol) was added to a solution of compound **2** (0.503 g, 1.36 mmol) in toluene (30 mL) via syringe. The reaction mixture was stirred for 16 h at ambient temperature, after which the white powder was isolated by filtration. 1-(Dicyclohexylphosphino)-3-trimethylammonium-methylindole iodide (0.67 g, 96%) was obtained by washing the solid with Et_2O (10 mL) and drying in vacuo; mp 202 °C (dec.). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.88 (s, 1 H, H2), 7.82 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H7), 7.72 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H4), 7.24 (t, $^3J_{HH}$ = 7.2 Hz, 1 H, H5), 7.20 (t, $^3J_{HH}$ = 7.2 Hz, 1 H, H6), 5.14 (s, 2 H, CH_2), 3.42 (s, 9 H, NMe_3), 2.29 (s, 2 H, Cy), 1.85 (br d, *J* = 8.3 Hz, 2 H, Cy), 1.72 (d, *J* = 11.4 Hz, 2 H, Cy), 1.61 (d, *J* = 8.3 Hz, 4 H, Cy), 1.36 (m, 4 H, Cy), 1.20 (m, 2 H, Cy), 1.05 (m, 6 H, Cy). ^{13}C NMR (150.8 MHz, DMSO-d_6): δ = 142.3 (s, C7a), 134.8 (s, C2), 128.9 (s, C4a), 122.7 (s, C5), 121.1 (s, C6), 118.9 (s, C7), 112.6 (s, C4), 106.2 (s, C3), 60.1 (s, CH_2), 51.6 (s, NMe_3), 35.1 (d, $^2J_{CP}$ = 15.0 Hz, PCH*C*H$_2$), 28.7 (d, $^1J_{CP}$ = 18.7 Hz, PCH), 27.6 (d, $^3J_{CP}$ = 6.1 Hz, PCHCH$_2$*C*H$_2$), 26.0 (d, $^2J_{CP}$ = 13.7 Hz, PCH*C*H$_2$), 25.8 (d, $^3J_{CP}$ = 7.5 Hz, PCHCH$_2$*C*H$_2$), 25.7 (s, PCHCH$_2$CH$_2$*C*H$_2$). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 55.2 (s). MS (ESI): *m/z* (%) = 326.2 (100) $[M – NMe_3]^+$. Anal. Calcd for $C_{24}H_{38}N_2PI$: C, 56.25; H, 7.47; N, 5.47. Found: C, 56.28; H, 7.57; N, 5.40.

General Procedure for Suzuki–Miyaura Coupling Reactions (Thermal): Phenylboronic acid (50.6 mg, 0.415 mmol), $Pd_2(dba)_3$ (5.2 mg, 0.00566 mmol), ligand (0.0136 mmol), cesium carbonate (184.3 mg, 0.566 mmol), and aryl halide (0.377 mmol) were sequentially added to a 10-mL conical microwave vial in an inert atmosphere dry box. The mixture was suspended in $[P_{66614}][NTf_2]$ (1.0 mL) and degassed H_2O (0.6 mL) as appropriate (Tables 2 and 3) and

stirred for 48 h at 180 °C in the sealed vial immersed in an oil bath. The reaction mixture was diluted with Et_2O (1.0 mL) containing 1% decane and filtered through a pad of Celite. A 0.1-mL aliquot was diluted with Et_2O (0.9 mL) and analyzed by GC–FID. Yields reported are the average of triplicate trials.

General Procedure for Suzuki–Miyaura Coupling Reactions (Microwave): Phenylboronic acid (50.6 mg, 0.415 mmol), $Pd_2(dba)_3$ (5.2 mg, 0.00566 mmol), ligand (0.0136 mmol), cesium carbonate (184.3 mg, 0.566 mmol), and aryl halide (0.377 mmol) were sequentially added to a 10-mL conical microwave vial in an inert atmosphere dry box. The mixture was suspended in $[P_{66614}][NTf_2]$ (1.0 mL) and degassed H_2O (0.6 mL) as appropriate (Tables 2 and 3) and stirred for 3 h at 180 °C in the sealed vial in a Biotage Initiator microwave synthesizer. The reaction mixture was diluted with Et_2O (1.0 mL) containing 1% decane and filtered through a pad of Celite. A 0.1-mL aliquot was diluted with Et_2O (0.9 mL) and analyzed by GC–FID. Yields reported are the average of triplicate trials.

Crystallographic data (excluding structure factors) for **1a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 943804. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.Uk].

