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Synthesis of Monodentate Ferrocenylphosphines and Their Application to the Palladium-Catalyzed Suzuki Reaction of Aryl Chlorides

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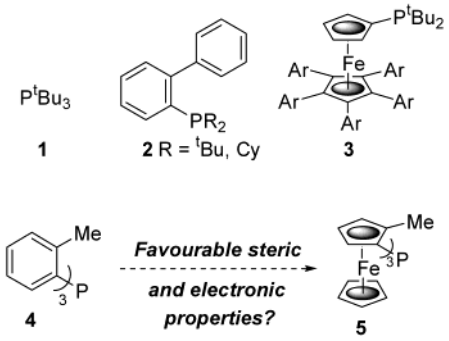
Racemic and enantiopure ($_pS$)-1-bromo-2-methylferrocene **6** were synthesized in 4 steps from 2-(4,4-dimethyloxazolinyl)ferrocene and (*S*)-2-(4-methylethyloxazolinyl)ferrocene, respectively (46 and 81% overall yield). Bromolithium exchange and addition of $ClPR_2$ gave the corresponding racemic or enantiopure 2-methylferrocenyl phosphine ligands 2-MeFcPR_2 **11** (R = Ph), **12** (R = Cy), and **13** (R = ^{t}Bu) in 28−93% yield. Use of PCl_3 gave the C_3-symmetric phosphine (2-MeFc)$_3$P **5** from ($_pS$)-**6** (72% yield) but racemic **6** did not lead to the formation of triferrocenyl phosphines. Combination of **5** and $Pd_2(dba)_3$ gave an active catalyst for the Suzuki reaction of aryl chlorides, for example, 4-chlorotoluene and phenylboronic acid reacted at only 60 °C in dioxane (86% yield). Other examples are reported together with the use of **12** in this same protocol. From the X-ray crystal structure of **5** the cone angle was determined as 211°. With this, and the electronic character of **11**, **12**, and other phosphines (derived from ν_{CO} of *trans*-[$(R_3P)_2$Rh(CO)Cl]), an analysis is made of the steric and electronic influences on ligand activity in the Suzuki reaction.

Introduction

Electron-rich and bulky monodentate phosphine ligands have recently been widely applied in palladium-catalyzed reactions of aryl halides. Most attention has focused on tri-*tert*-butylphosphine **1**,[1] biphenyls such as **2** containing di-*tert*-butylphosphino or dicyclohexylphosphino substituents,[2] and more recently pentaarylferrocene ligands **3**.[3] In conjunction with palladium these all generate catalysts capable of transforming aryl halide substrates in a variety of C−C coupling reactions (Suzuki,[1c,j,2a,c,d,l,3e] Heck,[1d,m,3b] Stille,[1i,n] Sonogashira,[1k] Negishi,[1l] enolate coupling,[1h,2f,h,k,j,3c,d]) in addition to C−O[1e,g,2b,i,3a,e] and C−N[1a,b,f,2c,e,3e] bond formation. These results have transformed the synthetic possibilities with low cost, low molecular weight aryl chlorides, and reactions of these substrates can often be carried out under very mild conditions.



One of the first uses of aryl chloride substrates in palladium-mediated C−C bond formation was with pal-

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ladacycles generated from tris(*o*-tolyl)phosphine **4** and related 2-methylphenyl-containing phosphines.[4] These results prompted a debate as to whether the structure of the palladacycle was maintained during the catalytic cycle, which would require the formation of palladium(IV) intermediates.[4a,b,5] Evidence now favors the palladacycles acting as sources of phosphine-ligated palladium(0).[6]

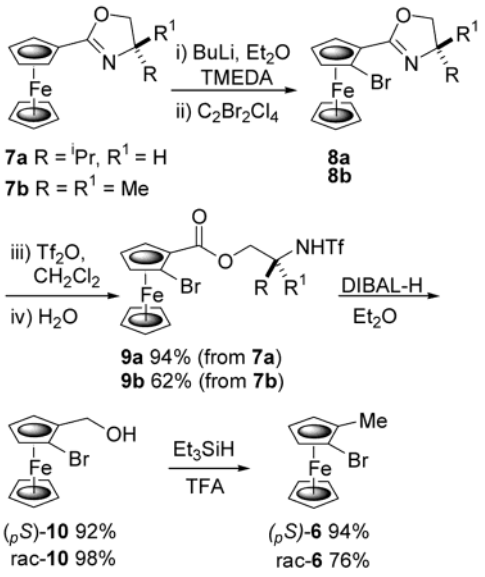
In light of these results we reasoned that tris(2-methylferrocenyl)phosphine **5**, the ferrocene equivalent of tris(*o*-tolyl)phosphine, would be a superior ligand for palladium-catalyzed transformations due to the greater size of ferrocene compared to benzene, and the possibility that ferrocene would have a favorable effect on the electronic properties of the attached phosphorus atom. This was reasoned from the ability of ferrocene to stabilize an adjacent positive charge; α-ferrocenylcarbenium ions are generally stable, isolable species.[7] Furthermore, one of the two possible diastereoisomers of **5** is C_3-symmetric. Enantiopure C_3-monodentate phosphine ligands are few in number and have been little studied in catalysis.[8] In view of the recent interest in monodentate phosphines,[9] a C_3-symmetric version is especially desirable, particularly if its symmetry properties may be combined with high activity in a resulting catalyst.

In this paper we report on the synthesis and application of **5** and related ligands to the palladium-catalyzed Suzuki reaction of aryl chlorides. The successful outcome is rationalized through an examination of the steric and electronic properties of the ligands, and contrasted to the properties of **1** and other ligands which display similar levels of reactivity. Parts of this work have been previously communicated.[10]

Results and Discussion

Ligand Synthesis. The most convenient approach to the desired ligand appeared to be from 1-bromo-2-methylferrocene **6** utilizing bromine−lithium exchange and addition of a phosphorus electrophile. As a consequence of the two different substituents this compound displays planar chirality. We[11] and others[12] have previously demonstrated the application of ferrocenyloxazolines to the synthesis of related 1,2-disubstituted ferrocene derivatives. Thus (*S*)-valine-derived oxazoline **7a**[11b] was subjected to highly diastereoselective lithiation (>100:1)[12c] followed by addition of dibromotetrachloroethane (Scheme 1). The resulting 2-bromoferrocenyloxazoline **8a** was found to be relatively unstable and was thus immediately ring-opened by treatment with triflic anhydride followed, after 5 min, by the addition of ice−water. The resulting ester **9a** was isolated in excellent overall yield with only a single diastereoisomer being observed by ^{1}H NMR spectroscopy. We have previously reported this ring-opening protocol for the synthesis of 1,1′,2,2′-tetrasubstituted ferrocenes.[13] The high yields obtained and the short reaction times make this method significantly more convenient than previously reported methods of ferrocenyloxazoline ring opening.[14] Reduction of **9a** to alcohol **10** was carried out with DIBAL-H. Use of lithium aluminum hydride resulted in partial removal of bromine to give hydroxymethylferrocene as an inseparable contaminant. Finally, ionic reduction[15] gave ($_pS$)-**6** in 81% overall yield. Racemic **6** was similarly synthesized from **7b**[16] (overall yield 46%).

SCHEME 1



Bromine−lithium exchange on ($_pS$)-**6** proceeded smoothly, and following addition of 0.33 equiv of phosphorus trichloride, the novel C_3-symmetric ligand ($_pS$,$_pS$,$_pS$)-**5** was isolated as an air-stable yellow crystalline solid (Scheme 2). This we named TomPhos after its first synthesizer. The identity of this new compound was confirmed by determination of its X-ray crystal structure (Figure 1). The unit cell contained two essentially identical C_3-symmetric structures with P−C bond lengths of 1.820(2) and 1.831(2) Å. These are at angles of 115.79°

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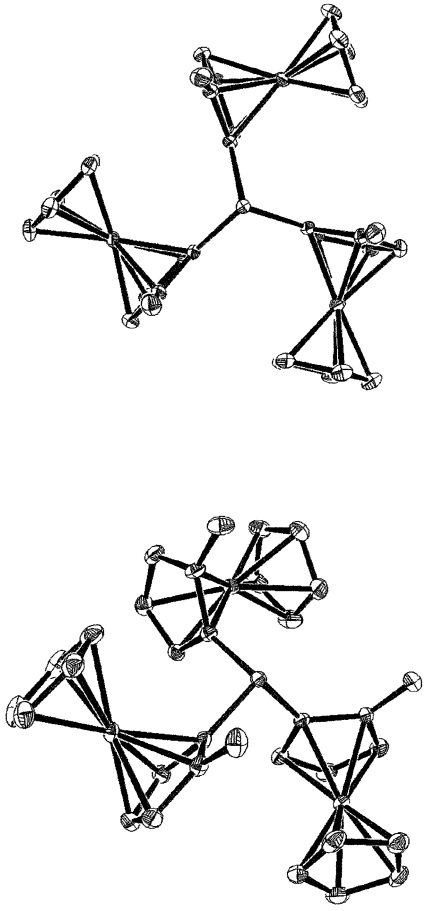
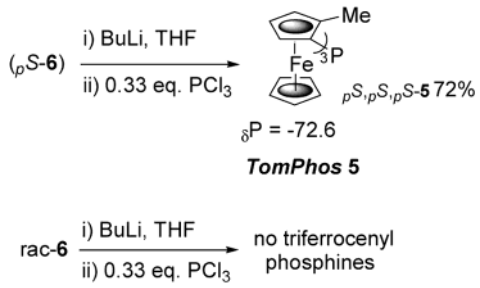


FIGURE 1. Two views of the X-ray structure determination of TomPhos **5**.

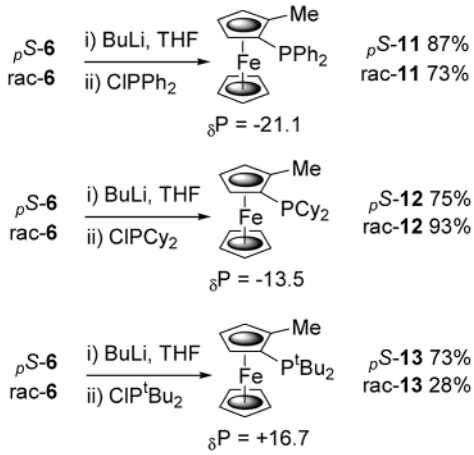
SCHEME 2



and 116.73° to their respective C_3-axes along which the phosphorus lone pairs are oriented. Relative to these C_3-axes the planes of the methyl-substituted cyclopentadienyl rings lie at angles of 10.46° and 9.18°. It is of note that in the ^{1}H NMR of **5**, the unsubstituted cyclopentadienyl ring is observed at δ 3.73 ppm, 0.46 ppm upfield of the corresponding value in ferrocene itself. This may be attributed to a positive anisotropic effect from adjacent methyl-substituted aromatic cyclopentadienyl rings.

Repeated attempts to use *rac*-**6** under the same conditions conspicuously did not result in the formation of $_pS$*,$_pS$*,$_pS$*-**5** or the other possible diastereoisomer with a $_pS$*,$_pS$*,$_pR$* configuration. Examination of the crude reaction mixture by ^{31}P NMR revealed a peak at 34.7 ppm, which we tentatively assigned to *meso*-chlorodi(2-methylferrocenyl)phosphine. The preferential and irreversible formation of this rather than the alternative

SCHEME 3



SCHEME 4

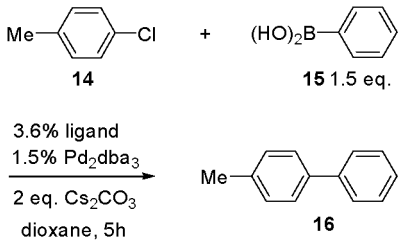


TABLE 1. Comparison of 5 and P^{t}Bu$_3$ in the Suzuki Cross-coupling of 14 and 15

entry	ligand	temp, °C	yield[a]
1	**5**	80	75 (75)[b]
2	P^{t}Bu$_3$	80	80 (95)
3	**5**	60	81 (86)
4	P^{t}Bu$_3$	60	74 (96)
5	P(*o*-tolyl)$_3$	60	<1
6	PFc$_3$	60	<1

[a] Determined by GC. [b] Yield after 24 h in parentheses

$_pS$*,$_pS$*-diastereoisomer, and its inability to react with the final equivalent of 2-lithio-1-methylferrocene, would account for the absence of both triferrocenyl phosphines.

Further monodentate ligands were generated from **6** by utilizing a series of commercially available chlorophosphines (Scheme 3). In this instance no significant difference was observed in the use of $_pS$- and *rac*-**6**, indicating little differences in the reactivity of enantiopure or racemic 2-lithio-1-methylferrocene intermediates.

Application to the Suzuki Reaction. To test our hypothesis that ligand **5** would be effective in palladium-catalyzed reactions, we examined the most widely used of these, the Suzuki coupling between an aryl halide and an aryl boronic acid. Fu and Littke had previously reported that P^{t}Bu$_3$/Pd$_2$(dba)$_3$ efficiently catalyzes the cross-coupling reaction between 4-chlorotoluene **14** and phenylboronic acid **15**,[1c] and we initially chose to compare **5** with P^{t}Bu$_3$ using these same conditions (Scheme 4, Table 1, entries 1 and 2).

This revealed **5** to be very similar to P^{t}Bu$_3$ with use of these previously optimized conditions. The only notable difference was the lack of further product formation in

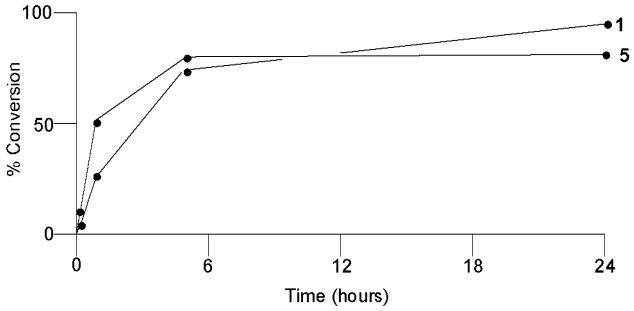


FIGURE 2. Graphical comparison of P^{t}Bu$_3$ **1** and TomPhos **5** in the formation of **16** at 60 °C.

TABLE 2. Analysis of the Variables in the Suzuki Cross-coupling of 14 and 15[a] Employing Ligand 5

entry	mol % of **5**	Pd source[b]	base[c]	solvent	% yield[d]
1	3.6	$Pd_2(dba)_3$	Cs_2CO_3[e]	dioxane	83 (94)[f]
2	6	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	89 (95)
3	3.6	$Pd_2(dba)_3$	CsF	dioxane	76 (91)
4	3.6	$Pd_2(dba)_3$	KF	dioxane	66 (71)
5	3.6	$Pd_2(dba)_3$	K_2CO_3	dioxane	43 (51)
6	3.6	$Pd_2(dba)_3$	Cs_2CO_3	THF	11 (11)
7	3.6	$Pd(OAc)_2$[g]	Cs_2CO_3	dioxane	41 (41)
8	3.6	$Pd(OAc)_2$[g]	Cs_2CO_3	THF	30 (51)

[a] 1.5 equiv. [b] 1.5 mol % unless otherwise stated. [c] Two equivalents unless otherwise stated. [d] Determined by GC. [e] Three equivalents. [f] Reaction time = 5 h (yield after 24 h in parentheses). [g] 3 mol %.

the reaction containing **5** after 24 h. This indicated that the catalyst generated from **5**/$Pd_2(dba)_3$ is very active but relatively short-lived, an observation consistent with the formation of palladium black after ~5 h. Lowering the reaction temperature to 60 °C improved the percentage conversion with **5**. In contrast, conversion with P^{t}Bu$_3$ is initially slower but a higher yield was obtained after 24 h (entries 3 and 4, Figure 2). Significantly, tris(*o*-tolyl)-phosphine **4** and tris(ferrocenyl)phosphine[17] both failed in this reaction, revealing the importance of the ferrocene groups and the methyl substituents to the activity observed with **5**.

We next sought to investigate the yield of this reaction as a function of the base, solvent, the source of palladium, and the amount of ligand employed (Table 2).

Increasing the amount of base (entry 1) or ligand (entry 2) led to an improvement in yield. It is of note that the ligand could be quantitatively recovered from these reactions and we never observed the formation of a palladacycle. Separate attempts to form a palladacycle by heating just **5** with $Pd(OAc)_2$ in toluene only led to the deposition of palladium black.[4c] Cesium fluoride was equally effective as a base (entry 3), potassium fluoride less so (entry 4), and potassium carbonate gave only a moderate yield (entry 5). Changing to THF as solvent led to a dramatic decrease in yield (entry 6) as did employing a palladium(II) salt (entry 7 and 8). The changes in yield observed here as a function of these variables generally mirror the results obtained with other monodentate phosphine ligands employed for the Suzuki reaction. A notable exception is the preferred use of $Pd(OAc)_2$ in conjunction with biaryl ligands of type **2**.[2]

(17) Prepared by electrophilic substitution of ferrocene with Me_2NPCl_2: Sollett, G. P.; Peterson, W. R. *J. Organomet. Chem*. **1969**, *19*, 143.

TABLE 3. Application of Ligands 11−13 to the Suzuki Cross-coupling of 14 and 15[a] at 60 °C

entry	ligand[b]	base[c]	solvent	% yield[d]
1	**11**	Cs_2CO_3	dioxane	2 (2)[e]
2	**12**	Cs_2CO_3	dioxane	17 (31)
3	**13**	Cs_2CO_3	dioxane	25 (29)
4	**12**	Cs_2CO_3	THF	51 (64)
5	**12**	CsF	dioxane	20 (33)
6	**12**	CsF	THF	60 (69)

[a] 1.5 equiv. [b] 3.6 mol %. [c] Two equivalents. [d] Determined by GC. [e] Reaction time = 5 h (yield after 24 h in parentheses).

Using these optimized conditions we next tested ligands **11**−**13** in this same reaction (Table 3). The diphenylphosphine **11** was essentially inactive (entry 1), ligands **12** and **13** providing a moderate yield of cross-coupled material (entries 2 and 3). Due to the instability of di-*tert*-butyl ligand **13**, we instead used the very air-stable dicyclohexylphosphine ligand **12** for a brief examination of the influence of base and solvent. In this instance THF led to a significant increase in yield (entry 4), a trend mirrored when CsF was employed as base (entries 5 and 6).

We next sought to use **5** and **12** with a wider range of substrates, and in particular to delineate the limits of their applicability with sterically and electronically demanding substrates (Table 4, entries 1−5). In addition, coupling of 4-nitrochlorobenzene proceeded in high yield (entry 6), and **5** again proved more effective than **12** (compare entries 3 with 4, and 6 with 7). However, **12** proved to be extremely effective with aryl bromide substrates, two examples of which were coupled in quantitative yield (entries 8 and 9).

Rationalization of Ligand Activity. In light of the similar yields with P^{t}Bu$_3$ and **5** in palladium-catalyzed Suzuki reactions, we reasoned that comparing their steric and electronic properties would help delineate the relative importance of these two factors for ligand activity. The size of a ligand is most simply quantified through measurement of the Tolman cone angle.[18] Beginning with the X-ray structures of **5**, an additional atom was introduced with a bond length to phosphorus of 2.28 Å.[19] Measurement from the center of this new atom to the edge of the van der Waals radii of the methyl groups revealed the cone angles of the two structures to be 212° and 210°. These contrast with the value of 182° previously determined for P^{t}Bu$_3$.[18] The cone angles of **11**, **12**, and **13** were obtained by summation of the contributions from the individual phosphorus substituents (Table 5).

The electronic characteristics of phosphorus ligands have been extensively investigated by measurement of carbonyl stretching frequencies in metal carbonyl adducts. Data are available for $Ni(CO)_3PR_3$ complexes derived from nickel tetracarbonyl.[20] Due to the toxicity and limited availability of this compound we instead began with $[Rh(CO)_2Cl]_2$ and synthesized *trans*-diphosphine adducts **17** which have also been used to study ligand electronic characteristics (Scheme 5, Table 6).[21]

Use of P^{t}Bu$_3$, **5**, and **13** in this same test gave rise to an anomalous figure of ~1996 cm^{-1} in each case, and

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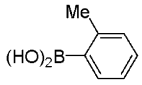
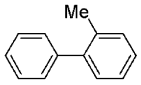
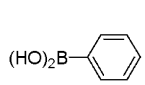
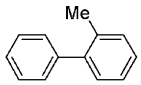
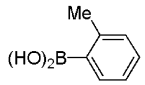
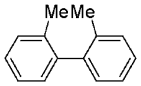
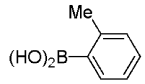
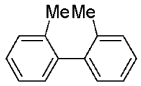
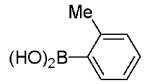
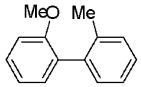
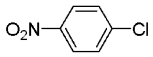
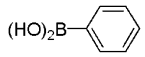
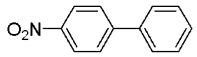
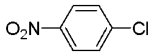
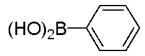
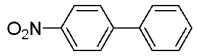
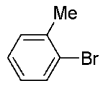
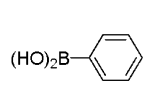
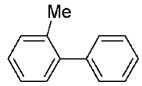
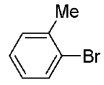
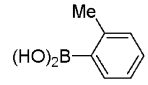
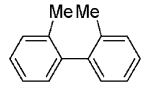
TABLE 4. Further Suzuki Cross-coupling Reactions with Ligands 5 and 12[a]

Entry	Aryl halide	Boronic acid	Ligand	Solvent	Product	Yield[b]
1			**5**	dioxane		57%
2			**5**	dioxane		49%
3			**5**	dioxane		46%
4			**12**	THF		18%
5			**5**	dioxane		36%
6			**5**	dioxane		90%
7			**12**	THF		75%
8			**12**	THF		100%
9			**12**	THF		100%

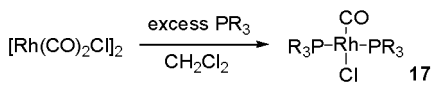
[a] 3.6 mol % of ligand, 1.5 mol % of Pd_2dba_3, 2 equiv of Cs_2CO_3, 60 °C, 5 h. [b] Determined by GC.

TABLE 5. Phosphine Ligand Cone Angles

phosphine	cone angle (deg)	contribution of substituents
PPh_3	145[a]	3 × 48.3
PCy_3	170[a]	3 × 56.7
P^tBu_3	182[a]	3 × 60.7
TomPhos **5**	211[b]	3 × 70.3
11	167	2 × 48.3 + 70.3
12	184	56.7 × 2 + 70.3
13	192	60.7 × 2 + 70.3

[a] From ref 20. [b] Average of the two values obtained.

SCHEME 5



these data were not used in the subsequent analysis. It has been shown that P^tBu_3 forms a Rh(I) complex **17** significantly distorted from the ideal square-planar geometry, preventing direct comparison of its carbonyl stretching frequency.[22]

The contribution from each phosphine substituent was calculated relative to the most basic phosphine in this series, tricyclohexylphosphine (Table 7). For comparison, previously reported values for $Ni(CO)_3PR_3$ complexes are also given, adjusted relative to PCy_3 (rather than P^tBu_3 as normally quoted). There is good agreement between the two series in the relative order of substituent contributions.

These figures reveal the ferrocenyl phosphines to be only slightly more electron rich than their phenyl analogues, but significantly electron poorer than trialkylphosphines. The X-ray crystal structure of **5** reveals the plane of the methyl-substituted cyclopentadienyl rings to lie almost perpendicular to the orbital occupied by the electron pair on phosphorus. Models reveal that this conformation, which minimizes the influence of filled metal-based orbitals (cf. the stabilization of α-ferrocenylcarbenium ions), is maintained in other ferrocenyl phosphines, such as **11**.

In Figure 3 the ligands used in this study are plotted against the steric and electronic parameters discussed

TABLE 6. Carbonyl Stretching Frequencies of Complexes 17

entry	ligand	ν(CO) of **17**[a] (cm^{-1})
1	PPh_3	1976.0[b]
2	P(*p*-tol)$_3$	1974.9
3	**11**	1974.2
4	Fc_3P	1973.0
5	P(*o*-tol)$_3$	1971.8
6	P(*o*-PhOMe)$_3$	1967.1
7	**12**	1956.0
8	P^nBu_3	1952.8
9	PCy_3	1948.5

[a] Determined in CH_2Cl_2. [b] 1967 cm^{-1} after solvent evaporation and redetermination as a Nujol mull (see ref 21).

(22) Harlow, R. L.; Westcott, S. A.; Thorn, D. L.; Baker, R. T. *Inorg. Chem.* **1992**, *31*, 323.

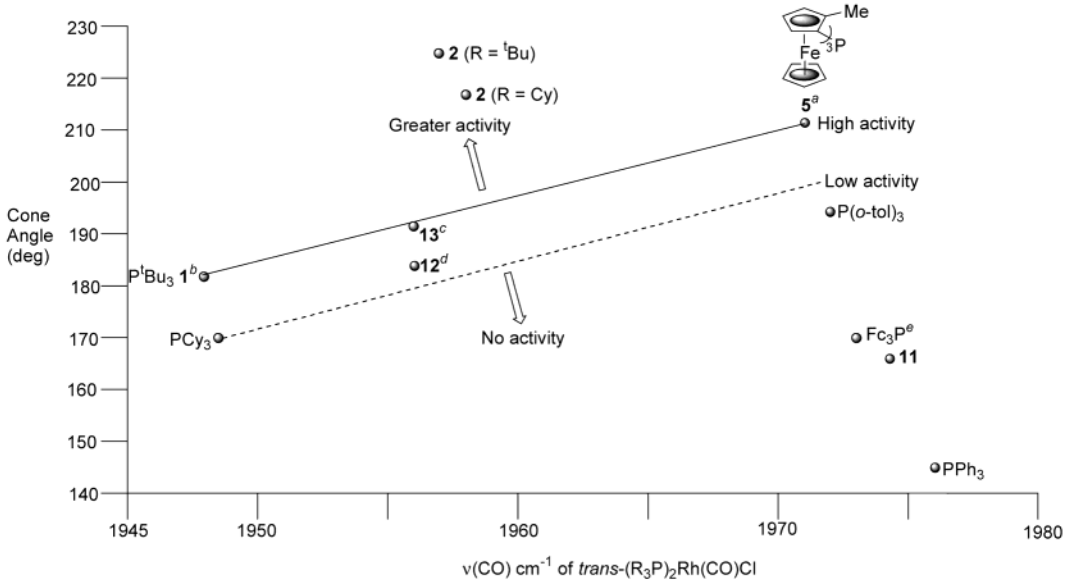


FIGURE 3. Analysis of ligand effectiveness in the Suzuki reaction of aryl chlorides as a function of size and electronic parameters. Notations: (a) ν(CO) estimated as 1971 cm^{-1}; (b) ν(CO) estimated as 1948 cm^{-1}; (c) ν(CO) estimated as 1956 cm^{-1}; (d) ν(CO) estimated as 1956 cm^{-1}; (e) cone angle determined as 170° by modification of the X-ray structure of **5**.

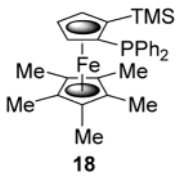
TABLE 7. Contribution of Individual Phosphine Substituents to Metal Carbonyl Stretching Frequencies

R	*trans*-$(R_3P)_2Rh(CO)Cl$ **17** (cm^{-1})	$Ni(CO)_3PR_3$[c] (cm^{-1})
^{t}Bu		−0.1
Cy	0	0
^{n}Bu	0.7[a]	1.3
o-PhOMe	3.1[a]	0.9
2-MeFc	3.7[b]	
o-tol	3.9[a]	3.5
Fc	4.1[a]	
Ph	4.6[a]	4.3

[a] [ν(CO) $(R_3P)_2Rh(CO)Cl$ − 1948.5]/6. [b] Average of the values determined from **11** and **12**. [c] From ref 20.

above. On the basis of the similar outcome observed with P^{t}Bu$_3$ and **5**, a line linking these two differing structures denotes the characteristics of active ligands for the palladium-catalyzed Suzuki reaction of aryl chlorides at 60 °C. Less effective ligands PCy_3[1c] and **12** fall in the zone of reduced activity, while other ligands such as P(*o*-tol)$_3$, Fc_3P, and PPh_3 are in the zone of inactivity, as defined by the mild conditions used in this study. That the di-*tert*-butylferrocenylphosphine **13** was found to be less active than **5** may be due to in situ decomposition of this surprisingly unstable ligand. In addition, the simple summation of cone angles used here may give an overestimate for the mixed substituent ligands **11**−**13**. However, we have not yet been successful in obtaining X-ray crystal structures to further examine this possibility.

These results support the contention that both electronic factors and size are important to ligand activity. Oxidative addition to palladium is promoted by electron-rich phosphine ligands,[23] and increasing the steric bulk around the metal should accelerate the rate of reductive elimination.[24] Furthermore, the line linking P^{t}Bu$_3$ and **5** reveals that the very favorable electronic properties of the former may be off set against further increases in the size of the ligand, not withstanding the decrease in catalyst stability revealed in this study. In support of this analysis is the recent report on the use of the bulky diarylferrocenylphosphine **18** for Suzuki coupling of aryl chlorides at 70 °C.[25]



18

In addition, biaryl ligands **2** may also be analyzed by this approach. Using the data above, the electronic parameter is estimated as ca. 1957−1958 cm^{-1}, and molecular modeling[19] reveals the cone angles of **2** (R = ^{t}Bu and Cy) to be approximately 225° and 217°, respectively (the contribution from the 2-biphenyl unit being 104°). These fall into the zone of higher activity compared to P^{t}Bu$_3$ and **5**, which correlates to the lower reaction temperatures required for Pd/**2**-catalyzed Suzuki coupling of aryl chlorides (room temperature for the reaction between **14** and **15**[2d]).

Conclusions

Enantiopure ($_pS$)-1-bromo-2-methylferrocene **6** is readily synthesized and is a key intermediate in the synthesis of planar chiral monodentate phosphine ligands, notably C_3-symmetric ($_pS$,$_pS$,$_pS$)-tris(2-methylferrocenyl)phosphine **5** (TomPhos). Combination with $Pd_2(dba)_3$ generates a very active catalyst for the Suzuki cross-coupling reaction. From an X-ray crystal structure analysis, the cone angle of **5** was determined as 211°. Analysis of 2-methylferrocenylphosphines **11** and **12** through formation of rhodium−carbonyl adducts, and comparison to

(23) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.
(24) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232.
(25) Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408.

other triaryl and trialkyl phosphine adducts, revealed the 2-methylferrocenyl group to be a typical aryl substituent. So the activity of the palladium(0) catalyst incorporating **5** is mainly a consequence of the ligand's size. Furthermore, no palladacycle could be obtained from **5**. This supports other evidence that palladacycles derived from 2-methylphenylphosphines are not involved in the catalytic cycles of the Suzuki reaction and related processes (requiring Pd(IV) intermediates). Finally, the similar activity of palladium catalysts containing P^tBu_3 and **5**, and their contrasting steric and electronic properties, was used to construct a model of ligand effectiveness in the Suzuki reaction. Using this approach we could rationalize the higher activity associated with biphenyl ligands **2**, and we believe that this method of analysis will be useful in explaining the characteristics of other ligands, aiding their rational design.

In our ongoing work we are applying the ligands described herein to other reactions, particularly those in which their nonracemic properties may find application.[26]

Experimental Section

General Considerations. Dichloromethane and TMEDA were distilled from calcium hydride and THF and Et_2O were distilled from sodium benzophenone ketyl, all under an atmosphere of nitrogen. Petroleum ether refers to that fraction boiling in the range 40−60 °C. Column chromatography was performed on SiO_2 (40−63 μm).

(*S*,$_p$*S*)-2-Isopropyl-2-trifluoromethylsulfonamidoethyl 1-bromoferrocene-2-carboxylate (9a): A dark orange solution of **7a**[11b] (12.00 g, 40.4 mmol) and TMEDA (7.92 mL, 52.6 mmol) in dry Et_2O (150 mL) under nitrogen was cooled to −78 °C. To this mixture was added dropwise BuLi in hexanes (22.15 mL, 52.5 mmol), the reaction mixture darkening to red/brown. After stirring at −78 °C for 4 h, 1,2-dibromotetrachloroethane (26.29 g, 80.7 mmol) in Et_2O (50 mL) was added via cannula and the reaction mixture allowed to warm to room temperature overnight. The resultant mixture was quenched with H_2O, partitioned, and further extracted with Et_2O. The organic extracts were combined, washed with brine, and dried ($MgSO_4$) and the solvent was removed in vacuo to give crude (*S*,$_p$*S*)-2-(2′-(4′-isopropyl)oxazolinyl)-1-bromoferrocene **8a** as a brown amorphous solid: ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 7 Hz), 1.04 (3 H, d, 3 H, J = 7 Hz), 1.87 (1 H, sep, J = 7 Hz), 4.00−4.17 (2 H, m), 4.25 (5 H, s), 4.27 (1 H, t, J = 3 Hz), 4.28−4.35 (1 H, m), 4.59 (1 H, br s), 4.68 (1 H, br s).

This was taken up in CH_2Cl_2 (80 mL) and cooled to 0 °C. Trifluoromethane sulfonic anhydride (7.47 mL, 53.5 mmol) was added via syringe and the resulting deep blue mixture was stirred for 5 min. Ice−water (100 mL) was added and the mixture allowed to stand until the ice had melted. After separation, the aqueous layer was further extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. Column chromatography (30% EtOAc/petroleum ether) followed by recrystallization (petroleum ether/EtOAc) gave **9a** as fine yellow needles (20.04 g, 94%): Mp 147−148 °C. Anal. Calcd for $C_{17}H_{19}BrF_3FeNO_4S$: C, 38.80; H, 3.64; N, 2.66. Found: C, 39.15; H, 3.64; N, 2.64. $[\alpha]^{25}_D$ +34 (*c* 0.105, EtOH). IR (Nujol) ν_{max} 3217 (NH), 1703 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, d, J = 6.9 Hz), 1.12 (3 H, d, J = 6.9 Hz), 2.05−2.14 (1 H, m), 3.60−3.65 (1 H, m), 4.27 (5 H, s), 4.29 (1 H, dd, J = 3.8, 11.9 Hz), 4.43 (1 H, t, J = 2.7 Hz), 4.53 (1 H, dd, J = 4.4, 11.9 Hz), 4.73 (1 H, t, J = 1.6 Hz), 4.85 (1 H, dd, J = 1.6, 2.7 Hz), 5.49 (1 H, d, J = 9.6 Hz). ^{13}C{^{1}H} ($CDCl_3$) δ 19.4, 19.5, 30.9, 60.8, 64.7, 68.7, 70.3, 70.6, 72.9, 75.6, 78.7, 115.1, 118.3, 121.5, 124.7, 170.8. MS (*m*/*z*; APCI) 527 (M$^+$, 100%), 525 (M$^+$, 100%), 447 (20).

2,2-Dimethyl-2-trifluoromethylsulfonamidoethyl 1-bromoferrocene-2-carboxylate (9b): A dark orange solution of **7b**[16] (2.00 g, 7.1 mmol) in dry Et_2O (18 mL) under nitrogen was cooled to −78 °C. To this was added dropwise BuLi in hexanes (5.65 mL, 14.1 mmol), the reaction mixture turning red after the addition. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, then re-cooled to −78 °C. A solution of 1,2-dibromotetrachloroethane (4.60 g, 14.1 mmol) in dry Et_2O (25 mL) was then added via cannula and the reaction mixture allowed to warm to room temperature overnight. The resultant mixture was quenched with H_2O, partitioned, and further extracted with Et_2O. The organic extracts were combined, washed with brine, dried over Mg_2SO_4, and filtered, and the solvent was removed in vacuo to give **8b** as viscous brown oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (6 H, s), 3.90 (1 H, d, J = 13 Hz), 3.92 (1 H, d, J = 13 Hz), 4.12 (5 H, s), 4.16 (1 H, br s), 4.46 (1 H, br), 4.63 (1 H, br s).

This was taken up in CH_2Cl_2 (50 mL) and cooled to 0 °C. Trifluoromethane sulfonic anhydride (1.30 mL, 9.3 mmol) was added via syringe and the resulting deep blue mixture was stirred for 5 min. Ice−water (20 mL) was then added and the mixture stirred for 10 min. After separation, the aqueous layer was further extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried (Mg_2SO_4), and filtered, and the solvent was removed in vacuo. Column chromatography (25% EtOAc/petroleum ether) followed by recrystallization (EtOAc/hexane) gave **9b** as an orange crystalline solid (2.246, 62%): Mp 82−83 °C. Anal. Calcd for $C_{16}H_{17}BrF_3FeNO_4S$: C, 37.52; H, 3.35; N, 2.74. Found: C, 37.87; H 3.39; N, 2.63. IR (Nujol) ν_{max} 3231 (NH), 1701 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.55 (3 H, s), 1.57 (3 H, s), 4.21−4.26 (2 H, m), 4.30 (5 H, s), 4.44 (1 H, t, J = 2.7 Hz), 4.73 (1 H, br s), 4.88 (1 H, br s), 5.63 (1H, s). ^{13}C{^{1}H} ($CDCl_3$) δ 25.0, 25.2, 59.2, 60.9, 68.8, 70.2, 70.4, 72.7, 75.5, 78.3, 112.6, 116.7, 121.9, 126.3, 170.4. MS (*m*/*z*, FAB) 513 (M$^+$, 100%), 511 (M$^+$, 100%), 433 (38), 147 (75).

($_p$*S*)-1-Bromo-2-hydroxymethylferrocene (10): DIBAL-H (1 M) in hexanes (35.0 mL, 35 mmol) was added to a solution of **9a** (5.00 g, 9.5 mmol) in Et_2O (100 mL) at 0 °C. After stirring for 10 min, the reaction was quenched slowly with H_2O (100 mL) and extracted with Et_2O, the combined organic extracts were filtered through a glass sinter, washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Recrystallization (EtOAc/petroleum ether) gave ($_p$*S*)-**10** as a yellow crystalline solid (2.585 g, 92%): Mp 88−90 °C. Anal. Calcd for $C_{11}H_{11}BrFeO$: C, 44.79; H, 3.76. Found: C, 44.66; H, 3.62. $[\alpha]^{25}_D$ +8 (*c* 0.096, EtOH). IR (Nujol) ν_{max} 3227 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.65 (1 H, t, J = 5.5 Hz), 4.15 (1 H, t, J = 2.3 Hz), 4.22 (5 H, s), 4.27 (1 H, br s), 4.41 (1 H, dd, J = 5.2, 12.3 Hz), 4.49 (1 H, br s), 4.58 (1 H, dd, J = 5.0, 12.3 Hz). ^{13}C{^{1}H} ($CDCl_3$) δ 60.18, 66.99, 67.41, 71.04, 71.33, 79.90, 86.00. MS (*m*/*z*, FAB) 296 (M$^+$, 5%), 294 (M$^+$, 5%), 279 (100), 277 (100).

Using this procedure, **9b** (8.30 g, 16.2 mmol) and DIBAL-H (58.0 mL, 58 mmol) in Et_2O (166 mL), workup, and column chromatography (3% EtOAc/petroleum ether) gave *rac*-**10** as a yellow crystalline solid (4.68 g, 98%): Mp 63−64 °C.

($_p$*S*)-1-Bromo-2-methylferrocene (6): A solution of ($_p$*S*)-**10** (5.00 g, 17.0 mmol) and triethylsilane (5.42 mL, 34.0 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and TFA (5 mL, 65 mmol) was added. After stirring for 5 min, the reaction was quenched slowly with saturated aqueous $NaHCO_3$ (50 mL). After separation, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. Column chromatography (3% EtOAc/petroleum ether) gave ($_p$*S*)-**6** as an orange crystalline solid (4.45 g, 94%): Mp 82−83 °C. Anal. Calcd for $C_{11}H_{11}BrFe$: C, 47.36; H, 3.98. Found: C, 47.58; H, 3.76. $[\alpha]^{25}_D$ −27 (*c* 0.11,

(26) For applications of chiral variants of **2** to asymmetric transformations see: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051. (b) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

EtOH). ^{1}H NMR ($CDCl_3$) δ 2.06 (3 H, s), 3.99 (1 H, t, J = 2.5 Hz), 4.04 (1 H, br s), 4.14 (5 H, s), 4.36 (1 H, br s). $^{13}C\{^1H\}$ ($CDCl_3$) δ 21.52, 65.97, 67.17, 69.96, 71.63, 79.9. MS (*m*/*z*, APCI) 280 (M^+, 100%), 278 (M^+, 100%), 200 (90).

Using this procedure, *rac*-**10** (1.50 g, 5.1 mmol), triethylsilane (1.63 mL, 10.2 mmol), and TFA (1.5 mL, 19 mmol) in CH_2Cl_2 (8 mL) gave *rac*-**6** as a yellow crystalline solid (1.08 g, 76%): Mp 52−55 °C.

(*pS*,*pS*,*pS*)-Tris(2-methylferrocenyl)phosphine (5): A solution of (*pS*)-**6** (1.00 g, 3.6 mmol) in THF (10 mL) was cooled to −78 °C and BuLi (1.55 mL, 3.6 mmol) was added via syringe. After stirring for 30 min, phosphorus trichloride (97 μl, 1.1 mmol) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (3%EtOAc/petroleum ether) to give (*pS*,*pS*,*pS*)-**5** as a yellow solid (542 mg, 72%): Mp 238−240 °C. Anal. Calcd for $C_{33}H_{33}Fe_3P\cdot{}^1/_2H_2O$: C, 62.21; H, 5.38. Found: C, 62.19; H, 5.26. $[\alpha]^{20}_D$ −72 (*c* 0.22, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 2.35 (3 H, s), 3.73 (5 H, s), 4.24 (2 H, t, J = 2.3 Hz), 4.33 (1 H, d, J = 1.5 Hz). $^{13}C\{^1H\}$ ($CDCl_3$) δ 15.24 (d, J = 14.4 Hz), 68.41, 69.27, 70.60 (d, J = 5.2 Hz), 71.07 (d, J = 5.8 Hz), 81.19 (d, J = 6.3 Hz), 89.38 (d, J = 36.3 Hz). ^{31}P NMR ($CDCl_3$) δ −72.6. MS (*m*/*z*, APCI) 628 (M^+, 100), 429 (M − 2-MeFc, 82%).

(*pS*)- and *rac*-2-methyl-1-diphenylphosphinoferrocene (11): Method A. A solution of (*pS*)-**6** (0.500 g, 1.79 mmol) in THF (5 mL) was cooled to −78 °C and BuLi (0.78 mL, 1.8 mmol) was added via syringe. After stirring for 30 min, chlorodiphenylphosphine (0.35 mL, 1.9 mmol) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was taken up in dry petroleum ether (10 mL) and filtered via cannula. The solvent was removed and the residue distilled by Kugelrohr (∼150 °C, 0.1 mmHg) to give (*pS*)-**11** as a yellow oil (600 mg, 87%): $[\alpha]^{25}_D$ −263 (*c* 0.099, EtOH). ^{1}H NMR ($CDCl_3$) δ 2.04 (3 H, s), 3.57 (1 H, t, J = 0.98 Hz), 4.04 (5 H, s), 4.17 (1 H, t, J = 2.4 Hz), 4.34 (1 H, t, J = 1.6 Hz), 7.16−7.19 (2 H, m), 7.25−7.27 (3 H, m), 7.37−7.39 (3 H, m), 7.51−7.53 (2 H, m). $^{13}C\{^1H\}$ ($CDCl_3$) δ 14.4, 68.7, 70.1, 70.8, 72.7, 76.1, 89.9, 128.2, 128.5, 128.6, 128.6, 129.4, 132.5, 132.7, 135.3, 135.5, 137.9, 140.1. ^{31}P NMR ($CDCl_3$) δ −21.1. MS (*m*/*z*, APCI) 385 (M^+, 100%). High-resolution MS (*m*/*z*; ES): found for MH^+ 385.0808. $C_{23}H_{22}FeP$ requires 385.0808.

Method B. *rac*-**6** (0.200 g, 0.72 mmol), THF (2 mL), BuLi (0.27 mL, 0.7 mmol), and chlorodiphenylphosphine (0.14 mL, 0.8 mmol) were manipulated as described above. Following cannula filtration, the residue was column chromatographed (3% EtOAc/petroleum ether) to give *rac*-**11** as a yellow oil that crystallized on standing (0.200 g, 73%): Mp 159−160 °C. ^{1}H and ^{31}P NMR data were essentially identical with those of (*pS*)-**11**.

(*pS*)-2-Methyl-1-dicyclohexylphosphinoferrocene (12): Method A. A solution of (*pS*)-**6** (1.50 g, 5.4 mmol) in THF (15 mL) was cooled to −78 °C and BuLi (2.34 mL, 5.4 mmol) was added via syringe. After stirring for 30 min, chlorodicyclohexylphosphine (1.31 mL, 5.9 mmol) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was taken up in dry petroleum ether (20 mL) and filtered via cannula. The solvent was removed and the residue distilled by Kugelrohr (∼200 °C, 0.1 mmHg) to give (*pS*)-**12** a yellow oil (1.60 g, 75%): $[\alpha]^{25}_D$ −148 (*c* 0.065, EtOH). ^{1}H NMR ($CDCl_3$) δ 1.09−2.06 (21 H, m), 2.09 (3 H, s), 2.32−2.36 (1 H, m), 4.00 (1 H, t, J = 1.6 Hz), 4.06 (5 H, s), 4.12 (1 H, t, J = 2.3 Hz), 4.24 (1 H, br s). $^{13}C\{^1H\}$ ($CDCl_3$) δ 29.03, 29.84, 29.94, 30.20, 30.48, 31.88, 32.55, 33.91, 34.08, 35.71, 36.22, 38.06, 70.19, 71.53, 72.28, 73.49, 79.56, 91.79. ^{31}P NMR ($CDCl_3$) δ −13.5. MS (*m*/*z*, APCI) 397 (MH^+, 100%). High-resolution MS (*m*/*z*; ES): found for MH^+ 397.1747. $C_{23}H_{34}FeP$ requires 397.1747.

Method B. *rac*-**6** (0.200 g, 0.72 mmol), BuLi (0.27 mL, 0.7 mmol), and chlorodicyclohexylphosphine (0.19 mL, 0.9 mmol) in THF (4 mL) were manipulated as described above (for *rac*-**11**) to give *rac*-**12** (0.263 g, 93%). ^{1}H and ^{31}P NMR data were essentially identical with those of (*pS*)-**12**.

(*pS*)-2-Methyl-1-di-*tert*-butylphosphinoferrocene (13): Method A. A solution of (*pS*)-**6** (0.500 g, 1.79 mmol) in THF (5 mL) was cooled to −78 °C and BuLi (0.78 mL, 1.8 mmol) was added via syringe. After stirring for 30 min, chlorodi-*tert*-butylphosphine (0.38 mL, 2.0 mmol) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was taken up in dry petroleum ether (10 mL) and filtered via cannula. The solvent was removed and the residue distilled by Kugelrohr (∼250 °C, 0.1 mmHg) to give (*pS*)-**13** as a very air-sensitive brown/red oil (0.449 g, 73%): ^{1}H NMR ($CDCl_3$) δ 0.90 (9 H, d, J = 14.68 Hz), 1.47 (9 H, d, J = 15.96 Hz), 2.07 (3 H, s), 4.10 (5 H, s), 4.16 (1 H, t, J = 2.5 Hz), 4.30 (2 H, m). ^{31}P NMR ($CDCl_3$) δ 16.69. MS (*m*/*z*, APCI) 345 (MH^+, 100%). High-resolution MS (*m*/*z*, ES) found for $[M + OH]^+$ 361.1383. $C_{19}H_{30}FeOP$ requires 361.1384.

Using this procedure, *rac*-**9** (0.200 g, 0.72 mmol), BuLi (0.27 mL, 0.7 mmol), and chlorodi-*tert*-butylphosphine (0.13 mL, 0.7 mmol) in THF (2 mL) gave *rac*-**13** (0.07 g, 28%). ^{1}H and ^{31}P NMR data were essentially identical with those of (*pS*)-**13**. Method B was unsuccessful for the synthesis of **9**.

General Procedure for Suzuki Cross-coupling Experiments. All reactions were carried out using a Radleys Carousel attached to a Schlenk line. A solution of aryl chloride (0.63 mmol), boronic acid (0.95 mmol), Pd_2dba_3 (0.009 mmol), base (1.26 mmol), and phosphine ligand (0.023 mmol) in toluene, dioxane, or THF (2 mL) was stirred under nitrogen at the required temperature. Samples were taken via syringe (∼50 μL), diluted with CH_2Cl_2 (1 mL), and subjected to GC analysis.

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Supporting Information Available: Details of the X-ray structure determination of **5** and ^{1}H and ^{31}P NMR spectra of **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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