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Ferrocenyl Monophosphine Ligands: Synthesis and Applications in the Suzuki−Miyaura Coupling of Aryl Chlorides

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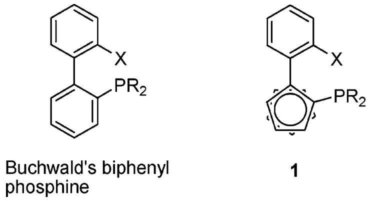
Abstract: Ferrocenyl monophosphine ligands have been developed by a method based on palladium-catalyzed Suzuki−Miyaura coupling. The modular procedure creates a rapid synthesis of phosphines with diverse properties. The electron-rich phosphines have been successfully applied to the Suzuki−Miyaura coupling of activated and deactivated aryl chlorides, with low catalyst loading being feasible in the synthesis of tris-*ortho*-substituted biaryls.

Palladium-catalyzed cross-coupling reactions have been extensively studied, dominating the catalytic transformations for C−C and C−heteroatom bond formation.[1] The efficient activation of aryl chlorides remains the goal in this area of study, due to their inexpensive costs and convenient availability.[2] In the specific case of Suzuki−Miyaura coupling, several classes of ligands have been developed that effect the coupling of activated and deactivated aryl chlorides; these include, for example, the electron-rich biaryl dialkylphosphines,[3] trialkylphosphines,[4] palladacycles,[5] carbenes,[6] and ferrocenylphosphines.[7] However, there are still few ligands available that allow for the coupling of deactivated aryl chlorides and boronic acids, both bearing *ortho* substituents, at a low catalyst loading.[3a,4b,5e] Herein, we report easy access to a class of monodentate ferrocenyl phosphine ligands, which are effective for the Suzuki−Miyaura coupling of deactivated aryl chlorides, including sterically hindered coupling partners, at a catalyst loading of 0.1 mol %.[8]

Recently, there has been a noteworthy emergence of ferrocenyl phosphines, providing suitable ligands for the palladium-catalyzed Suzuki−Miyaura coupling.[7] In our effort toward developing catalytic methods for phosphine synthesis,[9] we thought that *ortho*-arylated ferrocenyl phosphines **1** would provide good ligands for the Suzuki−Miyaura reactions on the basis of their similarity to Buchwald's biphenyl-based ligands.[3] Ligands **1** could be easily synthesized by an *ortho*-lithiation, an iodination, and a Suzuki−Miyaura coupling sequence starting with readily available ferrocenyl phosphine oxides. Some chiral analogues of **1** have recently been synthesized by Johannsen and a co-worker, starting with an optically pure ferrocenyl sulfoxide; the planar chiral dicyclohexylphosphines were shown to be effective in the Suzuki−Miyaura coupling of aryl chlorides at 2 mol % palladium loading and give moderate enantiomeric excesses in the asymmetric coupling of aryl bromides.[7a]



Ligands **1** can be synthesized in three steps from ferrocenyl phosphine oxides **2**, which were prepared by established methods (Scheme 1).[10] The first step is the *ortho*-lithiation of **2** to access the iodo-substituted phosphine oxides **3**. Price and Simpkins have previously

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SCHEME 1. **Modular Synthesis of Monoarylferrocenylphosphines**

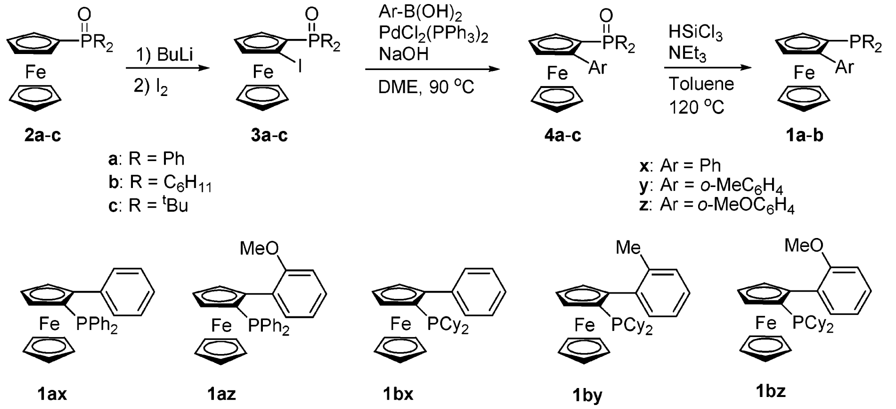
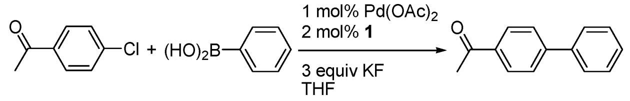


TABLE 1. **Suzuki−Miyaura Coupling of 4-Chloroacetophenone with Phenylboronic Acid**[a]



entry	ligand	T (°C)	conversion (%)[b]
1	**1ax**	22	40
2	**1az**	22	50
3	**1bx**	22	8
4	**1by**	22	11
5	**1bz**	22	61
6	**1ax**	65	22
7	**1az**	65	43
8	**1bx**	65	86
9	**1by**	65	96
10	**1bz**	65	100

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.5 equiv of arylboronic acid, 22 °C for 24 h or 65 °C for 11 h. [b] Conversion based on ^{1}H NMR.

reported the asymmetric *ortho*-lithiation of **2a** in the synthesis of a silylated ferrocenylphosphine oxide.[11] Using a combination of ^{n}BuLi and TMEDA, **3a** was obtained in 62% isolated yield. These conditions also allowed **3c** to be accessed, although the compound could not be isolated in an analytically pure form, as it did not appear to be stable to standard chromatographic purification. Compound **3b** required the alternative *ortho*-lithiation conditions developed by Snieckus and coworkers,[12] which utilize ^{t}BuLi as the source of lithium. Again, the iodo-substituted product could not be isolated in an analytically pure form. Because of their instability, compounds **3** were used without further purification.

The Suzuki−Miyaura reactions between compounds **3** and three arylboronic acids afforded the coupled oxides **4ax**,**az**, **4bx**−**bz**, and **4cx**−**cz** in good yields. The conditions were identical for each coupling reaction in that $PdCl_2(PPh_3)_2$ was used as the catalyst, with aqueous NaOH as the choice of base. With various arylboronic acids generally commercially available, the method should allow other *ortho*-arylated ferrocenyl phosphines or their oxides to be easily accessible, as we have previously demonstrated for biphenyl-based phosphines.[9d,g]

Free phosphines **1a**,**b** were easily obtained from oxides **4a**,**b** by reduction with trichlorosilane. By simply heating a mixture of **4a**,**b**, 5.0 equiv of $HSiCl_3$, and 5.5 equiv of NEt_3 in toluene at 90 °C, we obtained **1a**,**b** in analytically pure form in ca. 30% overall isolated yield. Unfortunately, we were unable to access (di-*tert*-butyl)phosphine **1c** using these conditions. Other attempts, including the choice of $LiAlH_4$ as the reducing agent, borane protection, and the use of higher temperatures, also proved unsuccessful.

With the ligands in hand, we began to examine their potential in coupling reactions. Ligands **1** were initially screened in the Suzuki−Miyaura coupling of an activated aryl chloride (4-chloroacetophenone) with phenylboronic acid. The analogous biphenylphosphines have previously been shown to be capable of activating Ar−Cl bonds at ambient temperatures.[3b] Using 1 mol % $Pd(OAc)_2$ and 2 mol % **1** at room temperature for 24 h, we were disappointed when a maximum of 61% conversion was obtained (Table 1, entries 1−5). At the elevated temperature of 65 °C, much improved conversions were observed, with **1b** at a reduced reaction time, however. This is in line with the literature where ferrocenyl ligands generally require heating to effect the Suzuki−Miyaura coupling of aryl chlorides.[7] In contrast, an adverse effect was observed with ligands **1a** (entries 6 and 7), indicating early catalyst decomposition. This preliminary screening established the more electron-rich phosphines **1b** to be superior to **1a** for coupling at high temperatures. Johannsen has reported that **1bz** delivers a >99% conversion at room temperature for the same coupling at 5 mol % palladium loading in wet THF with K_3PO_4 as the base in 24 h.[7a]

Ligands **1b** were then screened for the more demanding reaction between the deactivated 4-chlorotoluene and phenylboronic acid. Under conditions similar to those described above, using either KF or K_3PO_4 as a base, lower conversions resulted (Table 2, entries 1−6). However, switching to dioxane resulted in total or nearly total conversion with both bases when employing the more electron-rich and more sterically demanding **1by** and **1bz** (entries 7−12). Two equivalents of ligand appears necessary since using 1 equiv resulted in a reduced conversion (entry 13). This may be attributed to part of the phosphine being consumed in the reduction of Pd(II) to Pd(0).[13]

With the apparent improvement in performance with increased temperature, we decided to investigate the use

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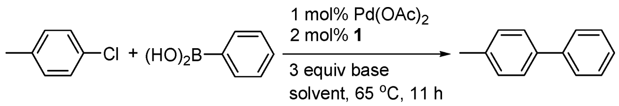
TABLE 2. Suzuki–Miyaura Coupling of 4-Chlorotoluene and Phenylboronic Acid[a]



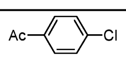
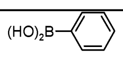
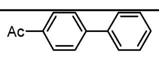
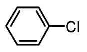
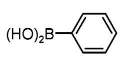
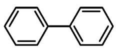
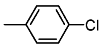
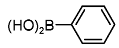
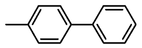
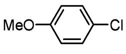
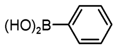
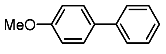
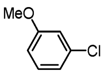
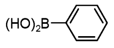
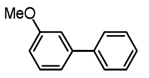
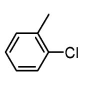
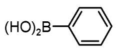
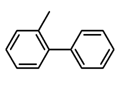
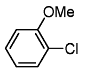
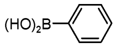
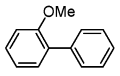
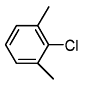
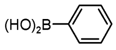
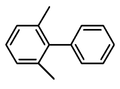
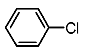
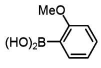
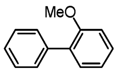
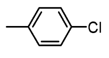
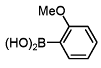
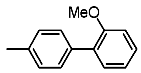
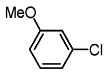
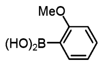
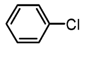
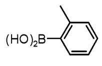
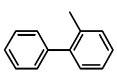
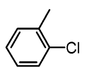
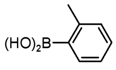
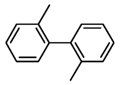
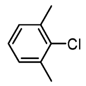
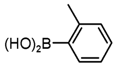
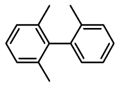
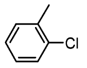
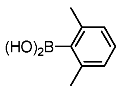
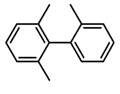
entry	ligand	solvent	base	conversion (%)[b]
1	**1bx**	THF	KF	64
2	**1bx**	THF	K_3PO_4	17
3	**1by**	THF	KF	71
4	**1by**	THF	K_3PO_4	73
5	**1bz**	THF	KF	61
6	**1bz**	THF	K_3PO_4	33
7	**1bx**	dioxane	KF	59
8	**1bx**	dioxane	K_3PO_4	62
9	**1by**	dioxane	KF	99
10	**1by**	dioxane	K_3PO_4	99
11	**1bz**	dioxane	KF	92
12	**1bz**	dioxane	K_3PO_4	100
13	**1by**	dioxane	K_3PO_4	86[c]

[a] Reaction conditions: 1.0 equiv of aryl chloride and 1.5 equiv of arylboronic acid. [b] Conversion based on ^{1}H NMR. [c] With 1 mol % **1by**, 24 h.

of lower catalyst concentrations. We were pleased to discover that 0.1 mol % Pd(OAc)$_2$ could be used at 95 °C to complete the same coupling using either **1by** or **1bz**. The scope of the reaction was successfully expanded to a range of aryl chlorides. As can be seen from Table 3, phenylboronic acid coupled with the activated 4′-chloroacetophenone and deactivated chlorotoluene and the anisole derivatives affording the corresponding biphenyls in excellent isolated yields regardless of the substitution pattern in the chlorides (entries 1–7). *ortho*-Substituted arylboronic acids coupled equally well with the deactivated chlorides (entries 9–12). The Suzuki–Miyaura coupling of aryl chlorides to access sterically bulky biaryls usually requires relatively high catalyst concentrations.[3a,4b,6b,c,7a,b,e] However, under the established conditions, bis-*ortho*-substituted biaryls could be made available in 89–90% yield (entries 8 and 13). Even a tris-*ortho*-substituted biaryl was accessed in 88% yield with the Suzuki–Miyaura coupling between 2-chloro-*m*-xylene and *o*-tolylboronic acid under these conditions (entry 14). However, some difficulty was encountered in accessing the same tris-*ortho*-substituted biaryl from 2-chlorotoluene and 2,6-dimethylphenylboronic acid, with a lower conversion observed, indicating the transmetalation step is more sensitive to the steric hindrance arising from the boronic acids (entry 15). Buchwald's bulky biaryl phosphines,[3a] Fu's PCy$_3$-based catalyst,[4b] and Glorius' flexible N-heterocyclic carbene[6c] appear to be the only known ligands capable of coupling in this manner (i.e., allowing bis-*ortho*-substituted arylboronic acids to be used) at catalyst loadings >1 mol %.

Encouraged, we decided to lower the catalyst concentration further to 0.01 mol % Pd(OAc)$_2$. However, for the reaction between 4-chlorotoluene and phenylboronic acid, the highest conversion obtained was 67%. This may be due to palladium decomposition before the palladium–phosphine catalyst is formed in situ in solution. In this sense, it is noted that the preformed palladacycle catalysts developed by Bedford are extremely effective for the Suzuki–Miyaura coupling of aryl chlorides with phenylboronic acid at very low catalyst loadings.[5a,b]

TABLE 3. Suzuki–Miyaura Coupling of Aryl Chlorides with Low Catalyst Loadings[a]

entry	aryl chloride	boronic acid	product	yield (%)[b]
1				87
2				97
3				94[c]
4				98[d]
5				91[e]
6				92[f]
7				95
8				89
9				87[e]
10				86[e]
11				93[e]
12				83
13				90[g]
14				88[e,g]
15				42[e,g,h]

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.5 equiv of arylboronic acid, 0.1 mol % Pd(OAc)$_2$, 0.2 mol % **1bz**, 3 equiv of K_3PO_4, dioxane, 95 °C, 24 h. Reaction times were not minimized. [b] Isolated yield. [c] Reaction conducted for 8 h. [d] With 0.4 mol % **1bz**. [e] With 0.2 mol % **1by** used as the ligand. [f] Reaction in toluene. [g] Reaction at 100 °C. [h] With 2.5 equiv of arylboronic acid.

Ligands **1b** are also effective for the Buchwald–Hartwig amination, a reaction that has become powerful

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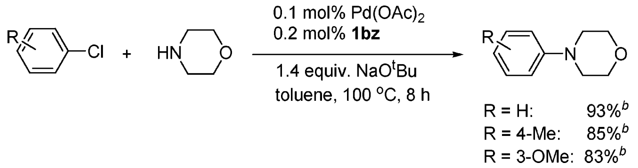
(13) (a) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

SCHEME 2. Amination of Aryl Chlorides with Low Catalyst Loadings[a]



[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of morpholine, and 1.4 equiv of NaO^{t}Bu. [b] Isolated yield.

for the preparation of substituted anilines.[2,14] Bulky, electron-rich phosphine and carbene ligands have frequently been employed for the less-reactive aryl chlorides.[15] We have found that **1bz** promotes the amination of aryl chlorides with morpholine at a low palladium loading of 0.1 mol %, furnishing the aniline derivatives in >80% isolated yields (Scheme 2).

To summarize, we have synthesized monoarylferrocenylphosphines via the Suzuki–Miyaura coupling of ferrocenyl phosphine oxides. This represents a simplified procedure for accessing such phosphines in that the easily accessible phosphine oxide itself serves as a directing group for *ortho*-lithiation rather than a more-expensive group that has to be cleaved afterward. The electron-rich phosphines **1b** have been demonstrated to be effective ligands for the palladium-catalyzed Suzuki–Miyaura coupling of aryl chlorides.

Experimental Section

General Procedure for the Suzuki Coupling of Arylboronic Acids with Iodo-Substituted Ferrocenylphosphine Oxides 3. To a Schlenk tube were added **3** (R = Ph, 2.0 mmol), arylboronic acid (4.0 mmol), and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol); the mixture was degassed. NaOH (1.67 mL, 3 M) and degassed DME (25 mL) were introduced, and the resulting mixture was heated at 90 °C for 24 h. After the mixture was cooled to ambient temperature, it was diluted with H_2O (25 mL) and extracted with $CHCl_3$ (3 × 25 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexane, 2:1) yielded the coupled products **4** in 49–86% yields.

General Procedure for the Suzuki Coupling of Aryl Chlorides at 0.1 mol % Catalyst Loading. An oven-dried carousel reaction tube was charged with boronic acid (1.5 mmol), K_3PO_4 (3 mmol), and phosphine **1** (2×10^{-3} mmol). The reaction vessel was evacuated and backfilled with N_2; this process was repeated five times. Through a rubber septum, aryl chloride in dioxane (1.0 mL, 1.0 M, 1.0 mmol), $Pd(OAc)_2$ in dioxane (0.5 mL, 2×10^{-3} M, 1×10^{-3} mmol), and dioxane (3.5 mL) were added to the reaction tube. The resulting mixture was heated at 95 °C for 24 h before being cooled to ambient temperature for analysis. Conversions were calculated from crude ^{1}H NMR, and isolated yields were obtained after a standard workup and purification by flash chromatography (hexane, 100%).

Acknowledgment. We thank the EPSRC (C.B.) and Johnson Matthey Synetix (J.X.) for support, and Johnson Matthey for the loan of palladium.

Supporting Information Available: Experimental procedures for the syntheses of **1**–**4**, procedures for the Suzuki–Miyaura coupling, and analytical data for the ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048963U

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(15) For some recent examples, see: (a) Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563. (b) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861. (c) Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479. (d) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978. (f) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.